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(54) Title: NOVEL HETEROCYCLES

(57) Abstract: The present invention relates to bone-targeting compounds useful for treating a variety of disorders and conditions, e.g., of bone tissue.

NOVEL HETEROCYCLES

Priority Information

The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application number 60/172,510, filed December 17, 1999, entitled "Bone Targeting Agents", U.S. Provisional Patent Application number 60/172,161, filed December 17, 1999, entitled "Proton Pump Inhibitors", and U.S. Provisional Patent Application number 60/240,788, filed October 16, 2000 entitled "Bone Targeting Agents", and the entire contents of each of these applications are hereby incorporated by reference.

The application further claims priority to U.S. National Patent Application number 09/741,619, entitled "Proton Pump Inhibitors", and U.S. National Patent Application number 09/740,653, entitled "Novel Purines", each of which is filed on even date herewith and is hereby incorporated by reference.

Background of the Invention

The need to treat debilitating bone disorders, such as osteoporosis, has led to extensive research on the mechanism and regulation of continuous bone formation and resorption. In particular, an appropriate balance of osteoblasts, which function to form bone tissue, and osteoclasts, which function to resorb bone tissue, is required to maintain the structural integrity and proper functioning of the skeleton in spite of continuous metabolism. Any changes in this balance of metabolism, such as an increased bone resorption (either absolute, or an increase via decreased bone formation relative to bone resorption) can lead bone diseases or disorders. One of the most common diseases resulting from this imbalance is osteoporosis, which is characterized by a decrease in bone mass and deterioration in skeletal micro-architecture leading to an increased fragility and susceptibility to fractures. Other diseases which result from alterations in bone resorption include, but are not limited to, Paget's Disease, primary and secondary hyperparathyroidism, humoral hypercalcemia of malignancy, various cancers where resorption is increased, and rheumatoid arthritis.

Because of the serious disorders that may result from a metabolic imbalance, researchers have been interested in studying bone metabolism, and the mechanism by which bone resorption and formation occurs, to ultimately develop a strategy for inhibiting resorption, and/or for improving bone mass and/or bone micro-architecture by stimulating osteoblast activity. However, the action of both osteoclasts and osteoblasts is controlled by a number of complex factors, and thus developing selective therapeutics has proven to be a difficult task.

One approach that has been taken for the development of novel therapeutics for bone disorders is inhibition of the osteoclast proton pump. Baron and coworkers have previously demonstrated that this proton pump is a vacuolar H^+-ATPase (see, Blair et al., *Science* **1989**, *245*, 855-857; Finbow et al., *Biochem. J.* **1997**, *324*, 697-712; Forgac, M. *Soc. Gen. Physiol. Ser.* **1996**, *51*, 121-132). It has been shown that osteoclasts, to effect bone resorption, ultimately lower the pH in the sealed microcompartment which underlies their site of attachment to the bone surface (see, Baron et al., *J. Cell. Biol.* **1985**, *101*, 2210-2222), thus resulting in the acidic envionment required to dissolve the bone mineral and to allow degradation of the bone matrix by proteases. The osteoclast uses a proton pump (an ATP-dependent transport of protons) to achieve this acidification and thus any therapeutic inhibition of the osteoclast proton pump should lead to a decrease in bone loss or turnover. As a result, many novel therapeutics developed to reduce bone resorption have focused on the inhibition of the proton pump to prevent osteoclast activity and excessive bone resorption. For a discussion of the vacuolar H^+-ATPase and inhibitors of vacuolar H^+-ATPase see Farina et al., *Exp. Opin. Ther. Patents* **1999**, *9*, 157-168 and David, P. and Baron, R. "The Vacuolar H^+-ATPase: A Potential Target for Drug Development in Bone Diseases" *Exp. Opin. Invest. Drugs* **1995**, *4*, 725-740.

In addition to the inhibition of the proton pump, studies have also been directed towards the control of signal transduction to ultimately affect osteoclast or osteoblast function. For example, studies have provided evidence that Src protein kinases play a cruical role in osteoclastic function, and it has been shown in different cell types that phosphorylation by Src, and related kinases, of proteins proposed to participate or regulate the cytoskeletal architecture is one important requirement for their proper function (see, for example, Missbach et al., "A Novel Inhibitor of the

Tyrosine Kinase Src Suppresses Phosphorylation of Its Major Cellular Substrates and Reduces Bone Resorption In Vitro and in Rodent Models In Vivo," *Bone* **1999**, *24*, 437-449). Because the cytoskeleton plays an important role in osteoclast motility, attachment, and formation of the sealing zone, it is likely that these cytoskeletal proteins may influence osteoclast function. Thus, agents which inhibit or promote interactions with Src or related kinases, are likely to affect cyctoskeletal proteins and ultimately affect osteoclast function. Several compounds have been reported as inhibitors of tyrosine Src kinase and thus are useful in the inhibition of osteoclast-mediated bone resorption (see, for example, Missbach et al., *Bone* **1999**, *24*, 437-449; Connolly et al., *Bioorg. & Med. Chem. Lett.* **1997**, *7*, 2415-2420; Trump-Kallmeyer et al., *J. Med. Chem.* **1998**, *41*, 1752-1763; Klutchko et al., *J. Med. Chem.* **1998**, *41*, 3276-3292; Legraverend et al., *Bioorg. & Med. Chem.* **1999**, *7*, 1281-1293; Chang et al., *Chem. & Biol.* **1999**, *6*, 361-375; Lev et al. *Nature* **1995**, *376*, 737-784; Palmer et al., *J. Med. Chem.* **1997**, *40*, 1519-1529.

As described above, many of the existing therapeutics that have been developed for the treatment of bone disorders such as osteoporosis are thought to act by inhibiting osteoclast activity. For example, estrogens, bisphosphonates, calcitonin, flavonoids, and selective estrogen receptor modulators are believed to act by the inhibition of osteoclast activity. Additionally, more recently, novel therapeutics have been developed to promote a fast increase in bone mineral content by promoting osteoblast activity. Such examples include peptides from the parathyroid hormone family, strontium ranelate, and growth hormone and insulin-like growth response (see, for example, Reginster et al. "Promising New Agents in Osteoporosis," *Drugs R & D* **1999**, *3*, 195-201). Unfortunately, a significant problem of many of these therapetic agents, however, is that they are not specific enough for bone tissue and thus may lead to unwanted adverse side effects.

Clearly, as evidenced by the number of different approaches to the available therapeutic agents, bone metabolism is controlled by a variety of factors. A common theme, however, is the desire to develop selective inhibitors or promoters of osteoclast or osteoblast activity, respectively. Although progress has been made towards developing therapeutic agents for osteoporosis and other bone disorders, there remains a need to develop potent and selective agents having minimal side effects.

Summary of the Invention

In general, the present invention provides compounds comprising a bone targeting moiety and a payload for the treatment or prevention of bone disorders and/or other conditions. In other embodiments, certain novel bone targeting moieties themselves, as described herein, also act as therapeutic agents for use in the treatment of bone disorders and/or other conditions. In certain other embodiments, the present invention provides compounds comprising a bone targeting moiety and a kinase inhibitor.

Thus, the present invention provides, in certain embodiments, compounds of Formula I, or pharmaceutically acceptable derivatives thereof.

In certain embodiments, a subject compound has the structure of Formula **(I)**:

Hc-X-K-Cy-L-Z-Tb

(I)

wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, such as $-CH_2-$, -CHF-, -CHOH-, -CH(Me)-, -C(=O)-, etc., or two M taken together represent substituted or unsubstituted ethene or ethyne;

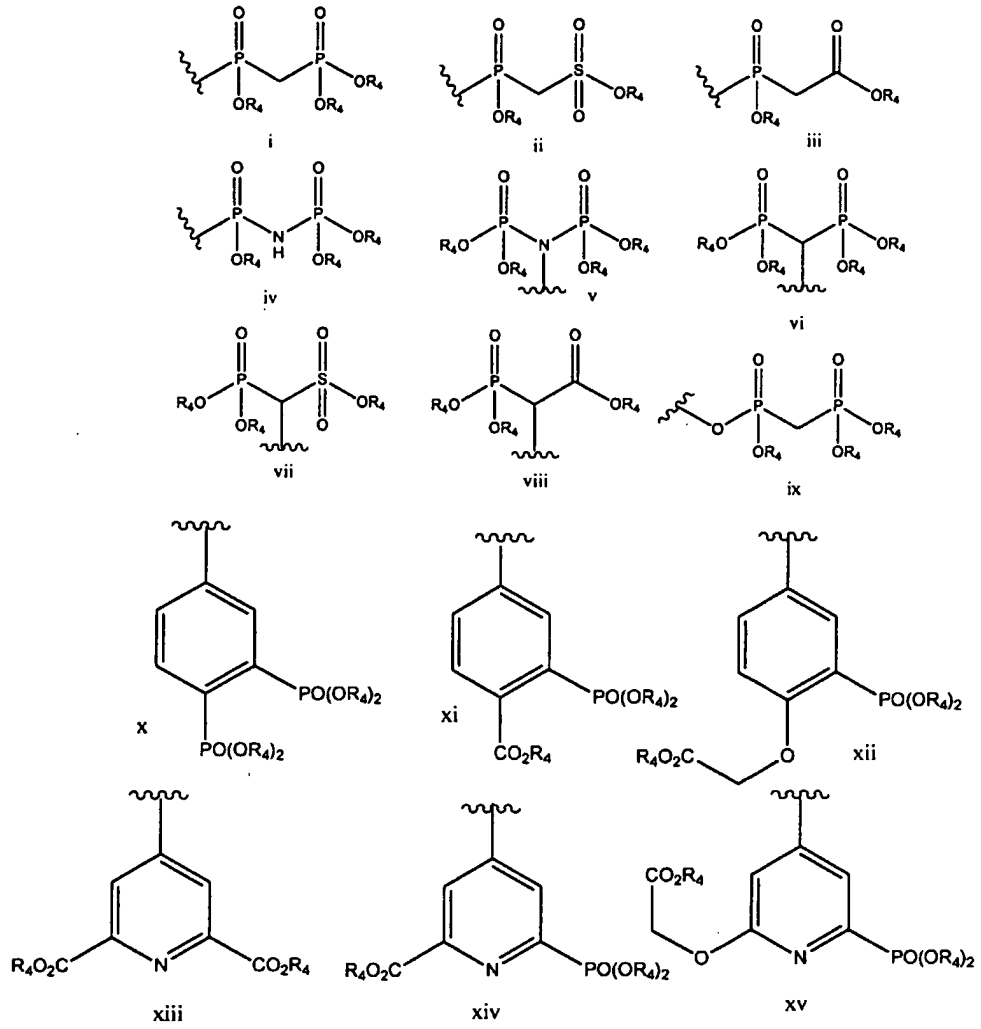
R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl or alkyl.

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl, including polycyclic groups;

p and n, independently, represent integers from 0-10, preferably from 0-5, even more preferably, from 0-3.

Hc represents a heterocycle, preferably a nitrogen-containing heterocycle; and

Tb represents a bone-targeting moiety preferably selected from:



wherein R_4 independently for each occurrence represents H or lower alkyl, preferably H or C_1-C_3 lower alkyl.

In embodiments wherein Tb is selected from i, v, vi, vii, viii, and ix, Z is preferably absent. In embodiments wherein Tb is selected from ii, iii, and iv, Z may be absent or represent O or NR. In embodiments wherein Tb is selected from x, xi, xii, xiii, xiv, and xv, Z may be absent or represent O or NR, preferably being absent.

In certain embodiments, R_4 represents H for all occurrences.

In certain embodiments, L represents alkyl-Y-alkyl, alkyl-Y-acyl, or alkyl.

In certain embodiments, the compound is free of hydrolyzable linkages. Hydrolyzable linkages, as the term is used herein, are saturated (sp^3-hybridized) carbons bound to two heteroatoms, of which at least one is selected from S, N, or O.

In certain embodiments, M represents a substituted or unsubstituted methylene group, such as $-CH_2-$, -CHF-, -CHOH-, -CH(Me)-, -C(=O)-, etc.

In certain embodiments, Cy represents a carbocycle or a nitrogen-bearing heterocycle. Cy is preferably uncharged.

In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In certain embodiments, Cy is phenyl.

In certain embodiments, K is absent.

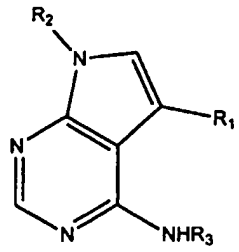
In certain embodiments, K represents alkyl-Y-alkyl, alkyl-Y-acyl, or alkyl.

In certain embodiments, Hc represents a bicyclic structure, preferably including heteroatoms in both rings. In certain embodiments, the ring(s) of Hc consist of C and N atoms. In certain embodiments, Hc represents a bicyclic heteroaryl structure.

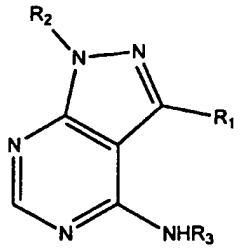
In certain embodiments, K is directly attached to a heteroatom of Hc, or X represents NR.

In certain embodiments, Hc includes at least one aryl substituent.

In certain embodiments, Hc-X taken together represent one of the following structures:

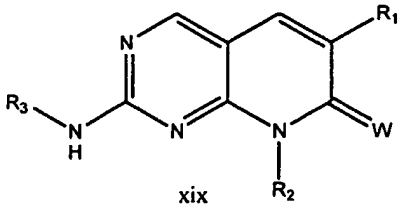


xvi

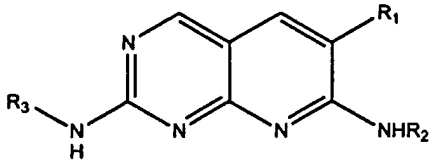


xvii

xviii



xix



xx

wherein W represents O or S, and one of R_1, R_2, and R_3 represents a bond to K, and the others represent, independently, hydrogen, halogen, alkyl, aralkyl, aryl, cycloalkyl, heteroaryl, heterocyclic, cycloalkyl, polycyclic, alkyl alkenyl, alkyl alkynyl, or alkanoyl, or taken together with the nitrogen to which it is attached, represent amidine, amide, carbamate, urea, or guanidine.

In certain embodiments wherein Hc-X is represented by xix or xx, R_3 represents a bond to K, R_2 is selected from hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, heteroaryl, heterocyclyl, cycloalkyl, polycyclyl, alkyl alkenyl, alkyl alkynyl, and alkanoyl; and R_1 is selected from hydrogen, halogen, aryl, and heteroaryl. In certain embodiments, R_2 is selected from hydrogen, $(CH_2)_nPh$, where Ph is phenyl or substituted phenyl and n is 0, 1, 2, or 3; heteroaryl, cycloalkyl, C_1-C_6 alkanoyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl groups may be substituted by NR_5R_6, phenyl, thioalkyl, alkyloxy, hydroxy, carboxy, halogen, cycloalkyl, and where R_5 and R_6 are independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(CH_2)_nPh$ where Ph is phenyl and n is 0, 1, 2, or 3; cycloalkyl, heteroaryl, and R_5 and R_6 taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen,

substituted nitrogen, oxygen and sulfur. In certain embodiments, R_1 is a substituted aryl moiety selected from of monohaloaryl, dihaloaryl, monomethylaryl, and dimethylaryl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Hc-X is represented by xvi or xvii, at least one of R_1, R_2, or R_3 represents a bond to K, R_3, if not a bond to K, is selected from hydrogen or alkyl, R_2, if not a bond to K, is selected from alkyl, cycloalkyl, alkyl alkenyl, alkyl alkynyl, and R_1, if not a bond to K, is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroalkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, or alkyl heterocyclyl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Hc-X is represented by xviii, R_2 represents a bond to K, and R_1 and R_3 are selected, independently, from hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroalkyl, heteroaralkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, and alkyl heterocyclyl. In certain embodiments, R_1 is alkyl or branched alkyl and R_3 is aryl, heteroaryl, or cycloalkyl. In certain embodiments, R_3 is selected from monohaloaryl, dihaloaryl, monohaloheteroaryl, dihaloheteroaryl, monohalocycloalkyl, or dihalocycloalkyl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Tb is represented by vii or viii, the compound is free of hydrolyzable linkages. In certain embodiments, L and K do not comprise nitrogen. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl,

cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments, Tb is represented by xi, xii, xiv, or xv. In certain embodiments, K and L do not include an amide bond, or are preferably free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, the compound does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by the moiety xiii, that moiety is not present in another portion of the compound, e.g., Hc is not xiii, etc. In certain embodiments, K does not include an amide bond, or is preferably free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, the compound does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl

([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by x, K does not include an amide bond, is free of carbonyls, is free of amine substituents, or is free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, the compound does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by ii, iii, iv, or v, the compound does not include a hydrolyzable linkage. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In certain

embodiments, K is directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by ix, Cy is preferably uncharged, and/or L-Cy-K is preferably free of hydrolyzable linkages. In certain embodiments, the compound is free of hydrolyzable linkages. In certain embodiments, Cy is preferably selected from aryl, carbocyclic, nitrogen-containing heterocyclic, and nitrogen-containing heteroaryl groups, and preferably does not include S or O atoms in the ring structure. In preferred embodiments, Cy contains 0 or 1 heteroatoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by i, Cy is preferably uncharged, and/or L-Cy-K is preferably free of hydrolyzable linkages. In certain embodiments, Cy is preferably selected from aryl, carbocyclic, nitrogen-containing heterocyclic, and nitrogen-containing heteroaryl groups, and preferably does not include S or O atoms in the ring structure. In preferred embodiments, the ring system of Cy contains 0 or 1 heteroatoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl

([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by i, Z and L are absent. In certain embodiments, Cy represents an aryl or heteroaryl group, such as a phenyl or pyridyl group. In certain embodiments, Cy is preferably uncharged, and/or the compound is preferably free of hydrolyzable linkages. In certain embodiments, Cy is preferably selected from aryl, carbocyclic, nitrogen-containing heterocyclic, and nitrogen-containing heteroaryl groups, and preferably does not include S or O atoms in the ring structure. In preferred embodiments, the ring system of Cy contains 0 or 1 heteroatoms, or is preferably phenyl. In certain embodiments, Hc represents heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb, where L and/or K is absent) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments of Formula I, Tb is selected from i and ix, and K is absent or represents -Y-, such as -NH-. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Cy is aryl or heteroaryl, preferably aryl. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent. In certain embodiments,

L represents alkyl, alkyl-Y-alkyl or alkyl-Y-acyl, wherein Y is preferably NR, such as NH or NMe.

In certain embodiments of Formula I, Tb is x and K is absent. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent. In certain embodiments, L represents alkyl, alkyl-Y-alkyl or alkyl-Y-acyl, wherein Y is preferably NR, such as NH or NMe.

In certain embodiments, a subject compound has the structure of Formula **(II)**:

Hc-X-K-Z-Tb

(II)

wherein Hc, X, K, Z, and Tb are as defined above.

In certain embodiments of Formula II, Tb is selected from x, xi, xii, xiii, xiv, and xv. In embodiments wherein Tb is selected from x, xi, xii, xiii, xiv, and xv, Z may be absent or represent O or NR, preferably being absent.

In certain embodiments, R_4 represents H for all occurrences.

In certain embodiments, the compound is free of hydrolyzable linkages. Hydrolyzable linkages, as the term is used herein, are saturated (sp^3-hybridized) carbons bound to two heteroatoms, of which at least one is selected from S, N, or O.

In certain embodiments, M represents a substituted or unsubstituted methylene group, such as $-CH_2-$, -CHF-, -CHOH-, -CH(Me)-, -C(=O)-, etc.

In certain embodiments, K is absent.

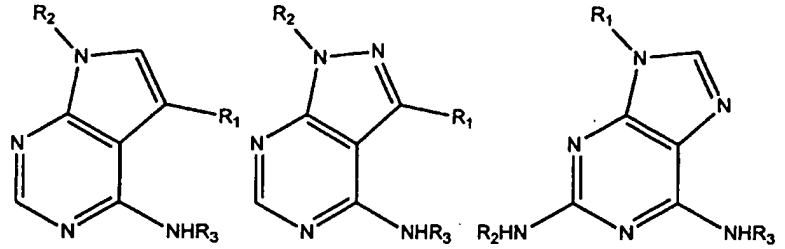
In certain embodiments, K represents alkyl-Y-alkyl, alkyl-Y-acyl, or alkyl.

In certain embodiments, Hc represents a bicyclic structure, preferably including heteroatoms in both rings. In certain embodiments, the ring(s) of Hc consist of C and N atoms.

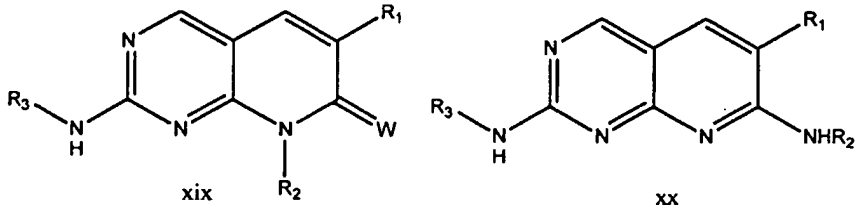
In certain embodiments, K is directly attached to a heteroatom of Hc, or X represents NR.

In certain embodiments, Hc includes at least one aryl substituent.

In certain embodiments, Hc-X taken together represent one of the following structures:



xvi xvii xviii



xix xx

wherein W represents O or S, and one of R_1, R_2, and R_3 represents a bond to K, and the others represent, independently, hydrogen, halogen, amidine, amide, carbamate, urea, guanidine, alkyl, aralkyl, aryl, cycloalkyl, heteroaryl, heterocyclic, cycloalkyl, polycyclic, alkyl alkenyl, alkyl alkynyl, or alkanoyl, or taken together with the nitrogen to which it is attached, represent amidine, amide, carbamate, urea, or guanidine.

In certain embodiments wherein Hc-X is represented by xix or xx, R_3 represents a bond to K, R_2 is selected from hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, heteroaryl, heterocyclyl, cycloalkyl, polycyclyl, alkyl alkenyl, alkyl alkynyl, and alkanoyl; and R_1 is selected from hydrogen, halogen, aryl, and heteroaryl. In certain embodiments, R_2 is selected from hydrogen, $(CH_2)_nPh$, where Ph is phenyl or substituted phenyl and n is 0, 1, 2, or 3; heteroaryl, cycloalkyl, C_1-C_6 alkanoyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl groups may be substituted by NR_5R_6, phenyl, thioalkyl, alkyloxy, hydroxy, carboxy, halogen, cycloalkyl, and where R_5 and R_6 are independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(CH_2)_nPh$ where Ph is phenyl and n is 0, 1, 2, or 3; cycloalkyl, heteroaryl, and R_5 and R_6 taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen and sulfur. In certain embodiments, R_1 is a substituted aryl moiety selected from of monohaloaryl, dihaloaryl, monomethylaryl, and dimethylaryl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Hc-X is represented by xviii, R_2 represents a bond to K, and R_1 and R_3 are selected, independently, from hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroalkyl, heteroaralkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, and alkyl heterocyclyl. In certain embodiments, R_1 is alkyl or branched alkyl and R_3 is aryl, heteroaryl, or cycloalkyl. In certain embodiments, R_3 is selected from monohaloaryl, dihaloaryl, monohaloheteroaryl, dihaloheteroaryl, monohalocycloalkyl, or dihalocycloalkyl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Hc-X is represented by xvi or xvii, at least one of R_1, R_2, or R_3 represents a bond to K, R_3, if not a bond to K, is selected from

hydrogen or alkyl, R_2, if not a bond to K, is selected from alkyl, cycloalkyl, alkyl alkenyl, alkyl alkynyl, and R_1, if not a bond to K, is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroalkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, or alkyl heterocyclyl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Tb is represented by vii or viii, the compound is free of hydrolyzable linkages. In certain embodiments, K does not comprise nitrogen. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments, Tb is represented by xi, xii, xiv, or xv. In certain embodiments, K does not include an amide bond, or are preferably free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, the compound does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by the moiety xiii, that moiety is not present in another portion of the compound, e.g., Hc is not xiii, etc. In certain embodiments, K does not include an amide bond, or is preferably free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, the compound does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is

absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by x, K does not include an amide bond, is free of carbonyls, is free of amine substituents, or is free of nitrogen atoms. In certain embodiments, the compound does not include a hydrolyzable linkage. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by ii, iii, iv, or v, the compound does not include a hydrolyzable linkage. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, K is directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by ix, the compound is preferably free of hydrolyzable linkages. In certain embodiments, the compound is free of hydrolyzable linkages. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

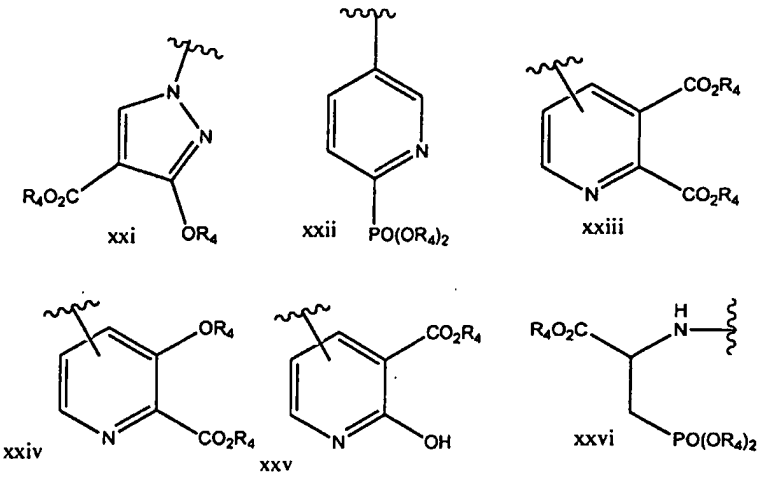
In certain embodiments wherein Tb is represented by i, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In

certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments of Formula II, Tb is selected from i and ix, and K is branched or unbranched alkyl. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent.

In certain embodiments of Formula II, Tb is xii, and K is absent or represents -Y-, such as -NH-. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent.

In certain embodiments of Formula II, Tb is x, and K represents alkyl or -Y-. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent. In certain embodiments of Formula I or II, Tb represents



In still other embodiments of the present invention, pharmaceutical compositions are provided comprising any one of the compounds of the present invention, or a pharmaceutically acceptable derivative thereof, and one or more pharmaceutically acceptable excipients.

In yet other embodiments, compounds of the invention, or compositions containing such compounds are administered to cells or to animals, preferably to a mammal in need therof, as a method for treating bone disorders. In particular cases, it will be advantageous to carry out such inventive methods using a pharmaceutical composition comprising a bone targeted compound which is capable of inhibiting bone resorption. In other cases, it will be advantageous to carry out that method using a pharmaceutical composition comprising a bone targeted compound that specifically acts as a Src kinase inhibitor. In other cases, it will be advantageous to carry out that method using a bone targeted compound of the present invention having a payload attached thereto that is capable of treating bone disorders by other means.

In still other embodiments, it will be advantageous to carry out inventive methods using a pharmaceutical composition comprising a bone targeting moiety that, alone, is capable of effecting treatment of bone disorders by inhibiting bone resorption or by other means.

Definitions

As mentioned above, this invention provides a novel class of bone targeted compounds useful for the treatment of bone disorders, preferably by inhibition of bone resorption. Compounds of this invention include those of Formula I and Formula II, set forth herein, and are illustrated in part by the various classes, subgenera and subsets of compounds described above, and by the various subgenera and species disclosed elsewhere in the specification, claims and figures. It will be appreciated that inventive compounds may be provided in the form of an individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of stereoisomers.

Also included are pharmaceutically acceptable derivatives of the foregoing compounds, where the phrase "pharmaceutically acceptable derivative" denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of an inventive compound, or any other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a compound as otherwise described herein, or a metabolite or residue thereof, preferably one which is capable of inhibiting bone resorption. Pharmaceutically acceptable derivatives thus include among others pro-drugs. A pro-drug is a derivative of a compound, usually with significantly reduced pharmacological activity, which contains an additional moiety which is susceptible to removal in vivo yielding the parent molecule as the pharmacologically active species. An example of a pro-drug is an ester which is cleaved in vivo to yield a compound of interest. Pro-drugs of a variety of compounds, and materials and methods for derivatizing the parent compounds to create the pro-drugs, are known and may be adapted to the present invention. One technique for providing a prodrug of a compound of the present invention is described generally in Niemi et al., *J. Med. Chem.* **1999**, *42*, 5053-5058.

The terms "inhibition of bone resorption" or "inhibition of osteoclast activity" or "inhibition of Src kinase activity" preferably refer to specific inhibition. Any of a variety of in vivo or in vitro assays may be employed to assess the ability of inventive compounds and compositions to treat or prevent bone disorders and/or other conditions, and in particular to inhibit bone resorption and/or to inhibit Src tyrosine phosphorylation (see, for example, the Exemplification section, which describes a useful rabbit osteoclast assay for studying effects on bone resorption, and a useful Src kinase inhibition assay). In particularly preferred embodiments of the invention, the observed effects on bone metabolism are selective in that the inventive compounds or compositions do not exert significant negative effects on biological processes other than bone metabolism, or specifically bone resporption or Src kinase activity. For example, particularly preferred inventive compositions show specific inhibition of Src kinase activity as compared with the activity of non-Src kinanses, or kinases located at sites away from bone. In some cases, such specific inhibition may result from specific localization of the inventive composition to bone sites, so that compositions

delivered in vivo do not have the opportunity to inhibit processes that occur away from bone; in other cases, specific inhibition may be attributed to specific action of the inventive payload on the osteoclast activity or on Src kinase activity, as compared with other cells or kinases.

The term "payload" includes therapeutic agents (e.g., a small molecule, a drug, a radiotherapeutic atom, etc.), detectable labels (e.g., fluorescent, radioactive, radiopaque, etc.), or any other moiety desired to be delivered to a site of action (e.g., a bone or other site suffering an abnormal condition).

A "small molecule" as the term is used herein refers to an organic molecule of less than about 2500 amu, preferably less than about 1000 amu.

"Subject" shall mean a human or animal (e.g., rat, mouse, cow, pig, horse, sheep, monkey, cat, dog, goat, etc.).

A "target" shall mean an *in vivo* site to which targeted agents bind. A target may refer to a molecular structure to which a targeting moiety binds, such as a hapten, epitope, receptor, dsDNA fragment, carbohydrate, or enzyme. Alternativelyy or additionally, a target may be a type of tissue, e.g., bone. A preferred target is bone. In certain preferred embodiments, target cells include osteoclasts.

The term "targeting moiety" refers to any molecular structure which assists the inventive composition in localizing to a particular target area, entering a target cell(s), and/or binding to a target receptor. Preferred targeting moieties according to the present invention include bone targeting moieties, as described herein.

A "therapeutic agent" shall mean an agent capable of having a biological effect on a host. Preferred therapeutic agents are capable of preventing and/or treating one or more symptoms of a bone disorder, such as a metabolic bone disorder. Other preferred therapeutic agents are capable of preventing or treating other bone disorders or related conditions. Examples of therapeutic agents considered to be within the scope of the present invention include boron-containing compounds (e.g. carborane),

chemotherapeutic nucleotides, drugs (e.g., antibiotics, antivirals, antifungals), enediynes (e.g., calicheamicins, esperamicins, dynemicin, neocarzinostatin chromophore, and kedarcidin chromophore), heavy metal complexes (e.g., cisplatin), hormone antagonists (e.g., tamoxifen), non-specific (non-antibody) proteins (e.g., sugar oligomers), oligonucleotides (e.g., antisense oligonucleotides that bind to a target nucleic acid sequence (e.g., mRNA sequence)), peptides, photodynamic agents (e.g., rhodamine 123), radionuclides (e.g., I-131, Re-186, Re-188, Y-90, Bi-212, At-211, Sr-89, Ho-166, Sm-153, Cu-67 and Cu-64), toxins (e.g., ricin), and transcription-based pharmaceuticals. In one preferred embodiment of the present invention in which compositions are provided for treating or preventing the establishment or growth of a tumor, the therapeutic agent is a radionuclide, toxin, hormone antagonist, heavy metal complex, oligonucleotide, chemotherapeutic nucleotide, peptide, non-specific (non-antibody) protein, a boron compound or an enediyne. In a preferred embodiment in which compositions are provided for treating osteoporosis, the therapeutic agent is a Src kinase inhibitor, capable of inhibiting the overactivity of osteoclasts.

With respect to the compounds of the present invention, a named R group will generally have the structure which is recognized in the art as corresponding to R groups having that name. For the purposes of illustration, representative R groups as enumerated in the specification and claims of the present application are defined herein. These definitions are intended to supplement and illustrate, not preclude, the definitions known to those of skill in the art.

The term "independently selected" is used herein to indicate that the R groups can be identical or different.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from

3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), $-CF_3$, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, $-CF_3$, -CN, and the like.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group). Exemplary aralkyl groups include, but are not limited to, benzyl and more generally $(CH_2)_nPh$, where Ph is phenyl or substituted phenyl, and n is 1, 2, or 3.

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. Likewise,

"lower alkenyl" and "lower alkynyl" have similar chain lengths. Preferred alkyl groups are lower alkyls. In preferred embodiments, a substituent designated herein as alkyl is a lower alkyl.

The term "aryl" as used herein includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms *ortho*, *meta* and *para* apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and *ortho*-dimethylbenzene are synonymous.

The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 10-membered ring structures, more preferably 3- to 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine,

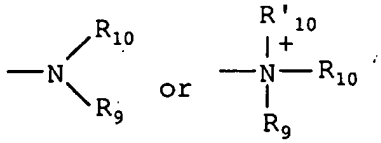
morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The terms "polycyclyl" or "polycyclic group" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The term "carbocycle", as used herein, refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

As used herein, the term "nitro" means $-NO_2$; the term "halogen" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means $-SO_2-$.

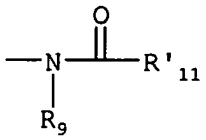
The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula:



wherein R_9, R_{10} and R'_{10} each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R_8$, or R_9 and R_{10} taken together with the N atom to which they

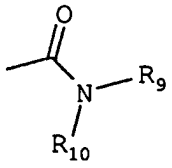
are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In preferred embodiments, only one of R_9 or R_{10} can be a carbonyl, e.g., R_9, R_{10} and the nitrogen together do not form an imide. In even more preferred embodiments, R_9 and R_{10} (and optionally R'_{10}) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(CH_2)_m-R_8$. Thus, the term "alkylamine" as used herein means an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of R_9 and R_{10} is an alkyl group.

The term "acylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



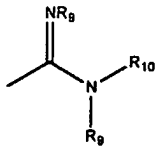
wherein R_9 is as defined above, and R'_{11} represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_8$, where m and R_8 are as defined above.

The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:



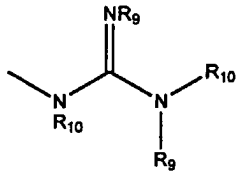
wherein R_9, R_{10} are as defined above. Preferred embodiments of the amide will not include imides which may be unstable.

The term "amidine" is art-recognized as a group that can be represented by the general formula:



wherein R_9, R_{10} are as defined above.

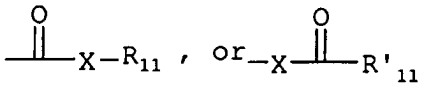
The term "guanidine" is art-recognized as a group that can be represented by the general formula:



wherein R_9, R_{10} are as defined above.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In preferred embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and -S-$(CH_2)_m$-R_8, wherein m and R_8 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

The term "carbonyl" is art recognized and includes such moieties as can be represented by the general formula:

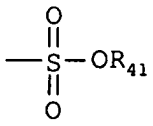


wherein X is a bond or represents an oxygen or a sulfur, and R_{11} represents a hydrogen, an alkyl, an alkenyl, -$(CH_2)_m$-R_8 or a pharmaceutically acceptable salt, R'_{11} represents a hydrogen, an alkyl, an alkenyl or -$(CH_2)_m$-R_8, where m and R_8 are as defined above. Where X is an oxygen and R_{11} or R'_{11} is not hydrogen, the formula represents an "ester". Where X is an oxygen, and R_{11} is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R_{11} is a hydrogen, the formula represents a "carboxylic acid". Where X is an oxygen, and R'_{11} is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X is a sulfur and R_{11} or R'_{11} is not hydrogen, the formula represents a "thiolester." Where X is a sulfur and R_{11} is hydrogen, the

formula represents a "thiolcarboxylic acid." Where X is a sulfur and R_{11}' is hydrogen, the formula represents a "thiolformate." On the other hand, where X is a bond, and R_{11} is not hydrogen, the above formula represents a "ketone" group. Where X is a bond, and R_{11} is hydrogen, the above formula represents an "aldehyde" group.

The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, $-O-(CH_2)_m-R_8$, where m and R_8 are described above.

The term "sulfonate" is art recognized and includes a moiety that can be represented by the general formula:



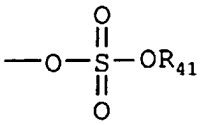
in which R_{41} is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in this list,

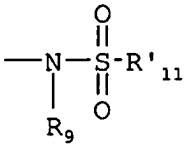
and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

The term "sulfate" is art recognized and includes a moiety that can be represented by the general formula:



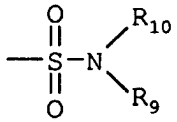
in which R_{41} is as defined above.

The term "sulfonamido" is art recognized and includes a moiety that can be represented by the general formula:



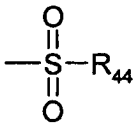
in which R_9 and R'_{11} are as defined above.

The term "sulfamoyl" is art-recognized and includes a moiety that can be represented by the general formula:



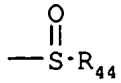
in which R_9 and R_{10} are as defined above.

The term "sulfonyl", as used herein, refers to a moiety that can be represented by the general formula:



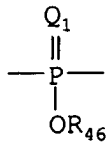
in which R_{44} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

The term "sulfoxido" as used herein, refers to a moiety that can be represented by the general formula:

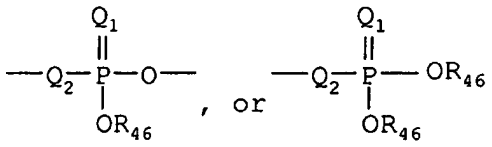


in which R_{44} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aralkyl, or aryl.

A "phosphoryl" can in general be represented by the formula:



wherein Q_1 represented S or O, and R_{46} represents hydrogen, a lower alkyl or an aryl. When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl can be represented by the general formula:



wherein Q_1 represented S or O, and each R_{46} independently represents hydrogen, a lower alkyl or an aryl, Q_2 represents O, S or N. When Q_1 is an S, the phosphoryl moiety is a "phosphorothioate".

As used herein, the definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991, incorporated herein by reference).

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g., bone targeting agents), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound in targeting bone. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

Detailed Description of Certain Preferred Embodiments of the Invention

As discussed above, there remains a need to develop selective and potent agents for treatment of bone disorders, preferably metabolic bone disorders. Thus, in general, the present invention provides compounds comprising a bone targeting agent and a payload for use in the treatment of bone disorders and other related disorders. In certain embodiments, the present invention provides compounds, pharmaceutical compositions and methods of selective treatment of metabolic bone disorders. In certain embodiments, these compounds and compositions are used to treat disorders

resulting from overactive osteoclast function. In certain other preferred embodiments, these compounds and compositions are used to treat osteoporosis.

Clearly, because of the numerous factors involved in bone metabolism, there are several approaches for the development of novel therapeutics. As described above, one approach would be to inhibit the activity of osteoclasts by inhibition of a proton pump, or by inhibition of Src tyrosine phosphorylation. Other approaches might involve the promotion of osteoblast activity. Irrespective of the approach taken, however, there remains a need for the development of selective and potent therapeutics capable of targeting bone tissue directly.

In view of this need for improved agents, the present invention provides novel compounds comprising a bone targeting moiety and a payload. Thus, in certain embodiments, the present invention contemplates the use of bone targeting agents, as described in more detail herein, having a specific payload attached thereto. The specific payload attached thereto may be useful in the inhibition of osteoclast activity via a proton pump, or via inhibition of Src tyrosine kinase, or via any other mechanism that affects the functioning of osteoclast or osteoblast cells. In certain other embodiments, the bone targeting agents themselves act as selective and potent inhibitors of osteoclast function.

Thus, the present invention, provides, in certain embodiments, compositions comprising a compound having the structure of Formula **(I)**:

Hc-X-K-Cy-L-Z-Tb

(I)

wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, such as $-CH_2-$, -CHF-, -CHOH-, -CH(Me)-, -C(=O)-, etc., or two M taken together represent substituted or unsubstituted ethene or ethyne;

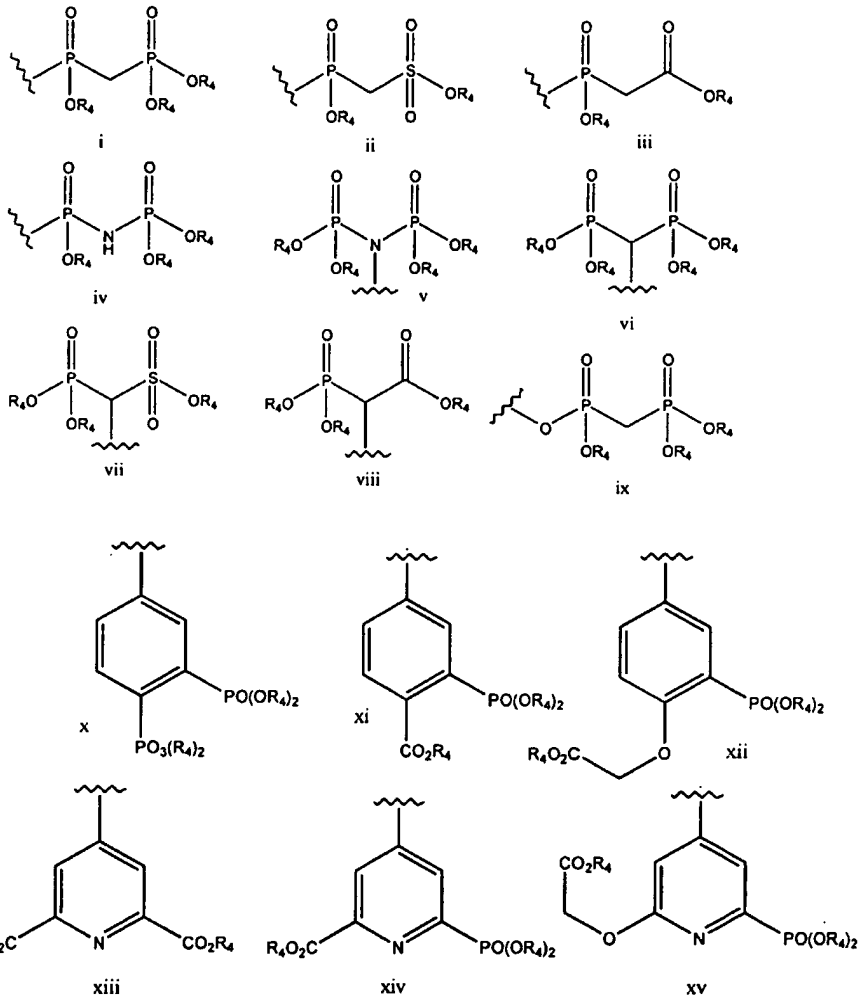
R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl or alkyl.

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl, including polycyclic groups;

p and n, independently, represent integers from 0-10, preferably from 0-5, even more preferably, from 0-3.

Hc represents a heterocycle, preferably a nitrogen-containing heterocycle; and

Tb represents a bone-targeting moiety preferably selected from:



wherein R_4 , independently for each occurrence, represents H, lower alkyl, or a pharmaceutically active small molecule or a prodrug form thereof, preferably H or C_1-C_3 lower alkyl.

In embodiments wherein Tb is selected from i, v, vi, vii, viii, and ix, Z is preferably absent. In embodiments wherein Tb is selected from ii, iii, and iv, Z may be absent or represent O or NR. In embodiments wherein Tb is selected from x, xi, xii, xiii, xiv, and xv, Z may be absent or represent O or NR, preferably being absent.

In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, an occurrence of R_4 represents $-CH_2OC(=O)$-(drug) or-$CH_2OC(=O)$-(prodrug).

In certain embodiments, L represents alkyl-Y-alkyl, alkyl-Y-acyl, or alkyl.

In certain embodiments, L-Cy-K-X-Hc is free of hydrolyzable linkages. Hydrolyzable linkages, as the term is used herein, are saturated (sp^3-hybridized) carbons bound to two heteroatoms, of which at least one is selected from S, N, or O.

In certain embodiments, M represents, independently for each occurrence, a substituted or unsubstituted methylene group, such as $-CH_2-$, -CHF-, -CHOH-, -CH(Me)-, -C(=O)-, etc.

In certain embodiments, Cy represents a carbocycle or a nitrogen-bearing heterocycle. Cy is preferably uncharged.

In certain embodiments, Cy is substituted with a second bone-targeting group (Tb), optionally through a linking group (such as -L-Z-).

In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In certain embodiments, Cy is phenyl.

In certain embodiments, K is absent.

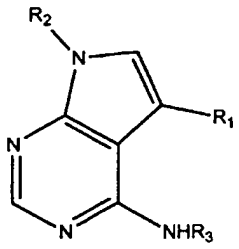
In certain embodiments, K represents alkyl-Y-alkyl, alkyl-Y-acyl, or alkyl.

In certain embodiments, Hc represents a bicyclic structure, preferably including heteroatoms in both rings. In certain embodiments, the ring(s) of Hc consist of C and N atoms. In certain embodiments, Hc represents a bicyclic heteroaryl structure.

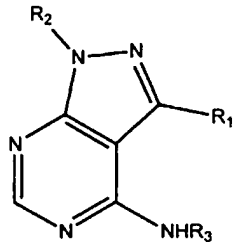
In certain embodiments, K is directly attached to a heteroatom of Hc, or X represents NR.

In certain embodiments, Hc includes at least one aryl substituent.

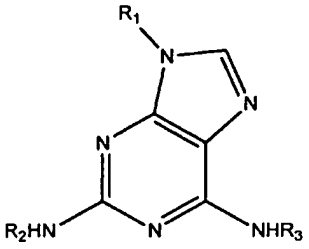
In certain embodiments, Hc-X taken together represent one of the following structures:



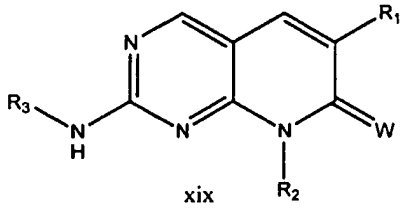
xvi



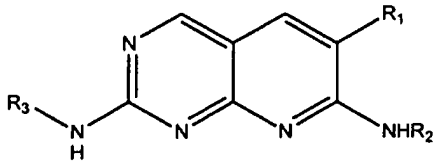
xvii



xviii



xix



xx

wherein W represents O or S, and one of R_1, R_2, and R_3 represents a bond to K, and the others represent, independently, hydrogen, halogen, alkyl, aralkyl, aryl, cycloalkyl, heteroaryl, heterocyclic, cycloalkyl, polycyclic, alkyl alkenyl, alkyl alkynyl, or alkanoyl, or taken together with the nitrogen to which it is attached, represent amidine, amide, carbamate, urea, or guanidine.

In certain embodiments wherein Hc-X is represented by xix or xx, R_3 represents a bond to K, R_2 is selected from hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, heteroaryl, heterocyclyl, cycloalkyl, polycyclyl, alkyl alkenyl, alkyl alkynyl, and alkanoyl; and R_1 is selected from hydrogen, halogen, aryl, and heteroaryl. In certain embodiments, R_2 is selected from hydrogen, $(CH_2)_nPh$, where Ph is phenyl or substituted phenyl and n is 0, 1, 2, or 3; heteroaryl, cycloalkyl, C_1-C_6 alkanoyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl groups may be substituted by NR_5R_6, phenyl, thioalkyl, alkyloxy, hydroxy, carboxy, halogen, cycloalkyl, and where R_5 and R_6 are independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(CH_2)_nPh$ where Ph is phenyl and n is 0, 1, 2, or 3; cycloalkyl, heteroaryl, and R_5 and R_6 taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen and sulfur. In certain embodiments, R_1 is a substituted aryl moiety selected from of monohaloaryl, dihaloaryl, monomethylaryl, and dimethylaryl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Hc-X is represented by xviii, R_2 represents a bond to K, and R_1 and R_3 are selected, independently, from hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroalkyl, heteroaralkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, and alkyl heterocyclyl. In certain embodiments, R_1 is alkyl or branched alkyl and R_3 is aryl, heteroaryl, or cycloalkyl. In certain embodiments, R_3 is selected from monohaloaryl, dihaloaryl, monohaloheteroaryl, dihaloheteroaryl, monohalocycloalkyl, or dihalocycloalkyl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Hc-X is represented by xvi or xvii, at least one of R_1, R_2, or R_3 represents a bond to K, R_3, if not a bond to K, is selected from hydrogen or alkyl, R_2, if not a bond to K, is selected from alkyl, cycloalkyl, alkyl alkenyl, alkyl alkynyl, and R_1, if not a bond to K, is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroalkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, or alkyl heterocyclyl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Tb is represented by vii or viii, L-Cy-K-X-Hc is free of hydrolyzable linkages. In certain embodiments, L and K do not comprise nitrogen. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments, Tb is represented by xi, xii, xiv, or xv. In certain embodiments, K and L do not include an amide bond, or are preferably free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, L-Cy-K-X-Hc does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one

substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by the moiety xiii, that moiety is not present in another portion of the compound, e.g., Hc is not xiii, etc. In certain embodiments, K does not include an amide bond, or is preferably free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, L-Cy-K-X-Hc does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by x, K does not include an amide bond, is free of carbonyls, is free of amine substituents, or is free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, L-Cy-K-X-Hc does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of

the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by ii, iii, iv, or v, L-Cy-K-X-Hc does not include a hydrolyzable linkage. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In certain embodiments, K is directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by ix, Cy is preferably uncharged, and/or L-Cy-K is preferably free of hydrolyzable linkages. In certain embodiments, L-Cy-K-X-Hc is free of hydrolyzable linkages. In certain embodiments, Cy is preferably selected from aryl, carbocyclic, nitrogen-containing heterocyclic, and nitrogen-containing heteroaryl groups, and preferably does not include S or O atoms in the ring structure. In preferred embodiments, Cy contains 0 or 1 heteroatoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K

is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by i, Cy is preferably uncharged, and/or L-Cy-K is preferably free of hydrolyzable linkages. In certain embodiments, Cy is preferably selected from aryl, carbocyclic, nitrogen-containing heterocyclic, and nitrogen-containing heteroaryl groups, and preferably does not include S or O atoms in the ring structure. In preferred embodiments, the ring system of Cy contains 0 or 1 heteroatoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by i, Z and L are absent. In certain embodiments, Cy represents an aryl or heteroaryl group, such as a phenyl or pyridyl group. In certain embodiments, Cy is preferably uncharged, and/or L-Cy-K-X-Hc is preferably free of hydrolyzable linkages. In certain embodiments, Cy is preferably selected from aryl, carbocyclic, nitrogen-containing heterocyclic, and nitrogen-containing heteroaryl groups, and preferably does not include S or O atoms in the ring structure. In preferred embodiments, the ring system of Cy contains 0 or 1 heteroatoms, or is preferably phenyl. In certain embodiments, Hc represents heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring

system, preferably having between 8 and 11 atoms, such as a fused cyclohexyl/cyclopentyl ([4.3.0]-bicyclononane) ring system. When Cy represents a fused ring system, one substituent of L and K (or Hc or Tb, where L and/or K is absent) may be attached to one of the two rings, and the other substituent to the other of the two rings. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments of Formula I, Tb is selected from i and ix, and K is absent or represents -Y-, such as -NH-. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Cy is aryl or heteroaryl, preferably aryl. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent. In certain embodiments, L represents alkyl, alkyl-Y-alkyl or alkyl-Y-acyl, wherein Y is preferably NR, such as NH or NMe.

In certain embodiments of Formula I, Tb is x and K is absent. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent. In certain embodiments, L represents alkyl, alkyl-Y-alkyl or alkyl-Y-acyl, wherein Y is preferably NR, such as NH or NMe.

In certain embodiments, a subject compound has the structure of Formula **(II)**:

Hc-X-K-Z-Tb

(II)

wherein Hc, X, K, Z, and Tb are as defined above.

In certain embodiments of Formula II, Tb is selected from x, xi, xii, xiii, xiv, and xv. In embodiments wherein Tb is selected from x, xi, xii, xiii, xiv, and xv, Z may be absent or represent O or NR, preferably being absent.

In embodiments wherein Tb is selected from i, v, vi, vii, viii, and ix, Z is preferably absent. In embodiments wherein Tb is selected from ii, iii, and iv, Z may be absent or represent O or NR.

In certain embodiments, R_4 represents H for all occurrences.

In certain embodiments, K-X-Hc is free of hydrolyzable linkages. Hydrolyzable linkages, as the term is used herein, are saturated (sp^3-hybridized) carbons bound to two heteroatoms, of which at least one is selected from S, N, or O.

In certain embodiments, M represents a substituted or unsubstituted methylene group, such as $-CH_2-$, -CHF-, -CHOH-, -CH(Me)-, -C(=O)-, etc.

In certain embodiments, K is absent.

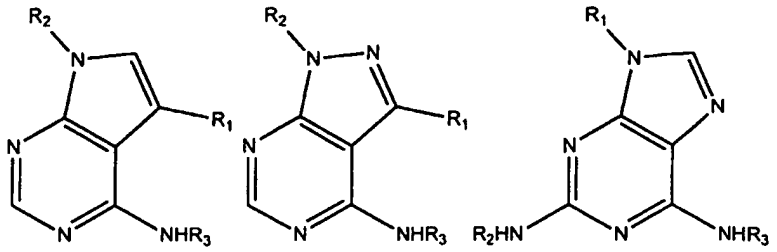
In certain embodiments, K represents alkyl-Y-alkyl, alkyl-Y-acyl, or alkyl.

In certain embodiments, Hc represents a bicyclic structure, preferably including heteroatoms in both rings. In certain embodiments, the ring(s) of Hc consist of C and N atoms.

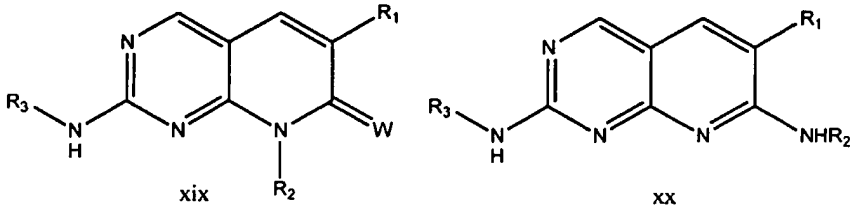
In certain embodiments, K is directly attached to a heteroatom of Hc, or X represents NR.

In certain embodiments, Hc includes at least one aryl substituent.

In certain embodiments, Hc-X taken together represent one of the following structures:



xvi xvii xviii



xix xx

wherein W represents O or S, and one of R_1, R_2, and R_3 represents a bond to K, and the others represent, independently, hydrogen, halogen, alkyl, aralkyl, aryl, cycloalkyl, heteroaryl, heterocyclic, cycloalkyl, polycyclic, alkyl alkenyl, alkyl alkynyl, or alkanoyl, or taken together with the nitrogen to which it is attached, represent amidine, amide, carbamate, urea, or guanidine.

In certain embodiments wherein Hc-X is represented by xix or xx, R_3 represents a bond to K, R_2 is selected from hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, heteroaryl, heterocyclyl, cycloalkyl, polycyclyl, alkyl alkenyl, alkyl alkynyl, and alkanoyl; and R_1 is selected from hydrogen, halogen, aryl, and heteroaryl. In certain embodiments, R_2 is selected from hydrogen, $(CH_2)_nPh$, where Ph is phenyl or substituted phenyl and n is 0, 1, 2, or 3; heteroaryl, cycloalkyl, C_1-C_6 alkanoyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl groups may be substituted by NR_5R_6, phenyl, thioalkyl, alkyloxy, hydroxy, carboxy, halogen, cycloalkyl, and where R_5 and R_6 are independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(CH_2)_nPh$ where Ph is phenyl and n is 0, 1, 2, or 3; cycloalkyl, heteroaryl, and R_5 and R_6 taken together with the nitrogen to which they are attached can complete a ring having 3 to 7 carbon atoms and optionally containing 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen and sulfur. In certain embodiments, R_1 is a substituted

aryl moiety selected from of monohaloaryl, dihaloaryl, monomethylaryl, and dimethylaryl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Hc-X is represented by xviii, R_2 represents a bond to K, and R_1 and R_3 are selected, independently, from hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroalkyl, heteroaralkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, and alkyl heterocyclyl. In certain embodiments, R_1 is alkyl or branched alkyl and R_3 is aryl, heteroaryl, or cycloalkyl. In certain embodiments, R_3 is selected from monohaloaryl, dihaloaryl, monohaloheteroaryl, dihaloheteroaryl, monohalocycloalkyl, or dihalocycloalkyl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Hc-X is represented by xvi or xvii, at least one of R_1, R_2, or R_3 represents a bond to K, R_3, if not a bond to K, is selected from hydrogen or alkyl, R_2, if not a bond to K, is selected from alkyl, cycloalkyl, alkyl alkenyl, alkyl alkynyl, and R_1, if not a bond to K, is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroalkyl, alkyl alkenyl, alkyl alkynyl, alkyl cycloalkyl, or alkyl heterocyclyl. In certain embodiments, at least one of R_1, R_2, and R_3, other than the bond to K, represents an aryl or heteroaryl substituent, preferably a substituted or unsubstituted phenyl.

In certain embodiments wherein Tb is represented by vii or viii, K-X-Hc is free of hydrolyzable linkages. In certain embodiments, K does not comprise nitrogen. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments, Tb is represented by xi, xii, xiv, or xv. In certain embodiments, K does not include an amide bond, or are preferably free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, K-X-Hc does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by the moiety xiii, that moiety is not present in another portion of the compound, e.g., Hc is not xiii, etc. In certain embodiments, K does not include an amide bond, or is preferably free of nitrogen atoms. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, K-X-Hc does not include a hydrolyzable linkage. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by x, K does not include an amide bond, is free of carbonyls, is free of amine substituents, or is free of nitrogen atoms. . In certain embodiments, K-X-Hc does not include a hydrolyzable linkage. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by ii, iii, iv, or v, K-X-Hc does not include a hydrolyzable linkage. In certain embodiments, Hc represents a

heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In certain embodiments, K is directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by ix, K-X-Hc is preferably free of hydrolyzable linkages. In certain embodiments, the compound is free of hydrolyzable linkages. In certain embodiments, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments wherein Tb is represented by i, Hc represents a heterocyclic bicycle. In certain embodiments, Hc represents a bicyclic heteroaryl structure. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, R_4 represents H for all occurrences. In embodiments wherein X is absent, K is preferably directly attached to a heteroatom of Hc. In certain embodiments, K is absent.

In certain embodiments of Formula II, Tb is selected from i and ix, and K is branched or unbranched alkyl. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent.

In certain embodiments of Formula II, Tb is xii, and K is absent or represents -Y-, such as -NH-. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent.

In certain embodiments of Formula II, Tb is x, and K represents alkyl or -Y-. In certain embodiments, Hc is selected from xvi, xvii, xviii, xix, and xx. In certain embodiments, Hc is further substituted with an aryl group, e.g., at a position of R_1, R_2, and R_3 not substituted with K. In certain embodiments, each of R_1, R_2, and R_3 represents a hydrocarbon substituent.

In certain embodiments, a subject compound has the structure of formula III: Tb-L-V, wherein Tb, R, and L are as defined above, and

V represents OR, NR_2, or SR.

In embodiments wherein Tb is selected from i, ii, iii, iv, v, vi, vii, viii, and ix, L is preferably not absent, and even more preferably represents alkyl. In certain embodiments, Tb represents i, ii, iii, or iv, preferably i. In certain embodiments, Tb represents v or vi. In certain embodiments, Tb represents vii or viii. In certain embodiments, Tb represents ix. In certain embodiments, V represents NR_2. In certain embodiments, all occurrences of R in V are H.

In certain embodiments, Tb is selected from x, xi, xii, xiii, xiv, xv, xxi, xxii, xxiii, xxiv, and xxv. In certain embodiments, Tb is selected from xi, xii, xiv, or xv. In certain embodiments, Tb is x. In certain embodiments, Tb is xiii. In certain embodiments, V represents NR_2. In certain embodiments, Tb is xxi, xxii, xxiii, xxiv, or xxv. In certain embodiments, Tb is xx. In certain embodiments, all occurrences of R in V are H. In certain embodiments, L represents lower alkyl or is absent.

In certain embodiments, a subject compound has the structure of Formula IV: Tb-Cy-L-V, wherein Tb, Cy, L, and V are as defined above, and Tb is selected from i, ii, iii, iv, v, vi, vii, viii, and ix. In certain embodiments, Tb represents i, ii, iii, or iv, preferably i. In certain embodiments, Tb represents v or vi. In certain embodiments, Tb represents vii or viii. In certain embodiments, Tb represents ix. In certain embodiments, L is absent. In certain embodiments, Cy represents a phenyl ring. In

certain embodiments, V represents NR_2. In certain embodiments, all occurrences of R in V are H. In certain embodiments, L represents lower alkyl or is absent.

In certain embodiments, a subject compound has the structure of Formula V: Tb-L-U, wherein Tb, R, and L are as defined above, and

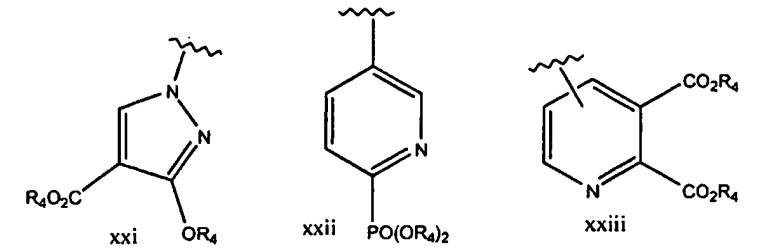
U represents a sulfonate ester (e.g., triflate, tosylate, mesylate, etc.), halogen (e.g., Cl, Br, I, preferably Br, I), formyl (CHO), or a suitable leaving group (e.g., a moiety whose conjugate acid, UH, has a pKa lower than 5, preferably lower than 0).

In embodiments wherein Tb is selected from i, ii, iii, iv, v, vi, vii, viii, and ix, L is preferably not absent, and even more preferably represents alkyl. In certain embodiments, Tb represents i, ii, iii, or iv, preferably i. In certain embodiments, Tb represents v or vi. In certain embodiments, Tb represents vii or viii. In certain embodiments, Tb represents ix.

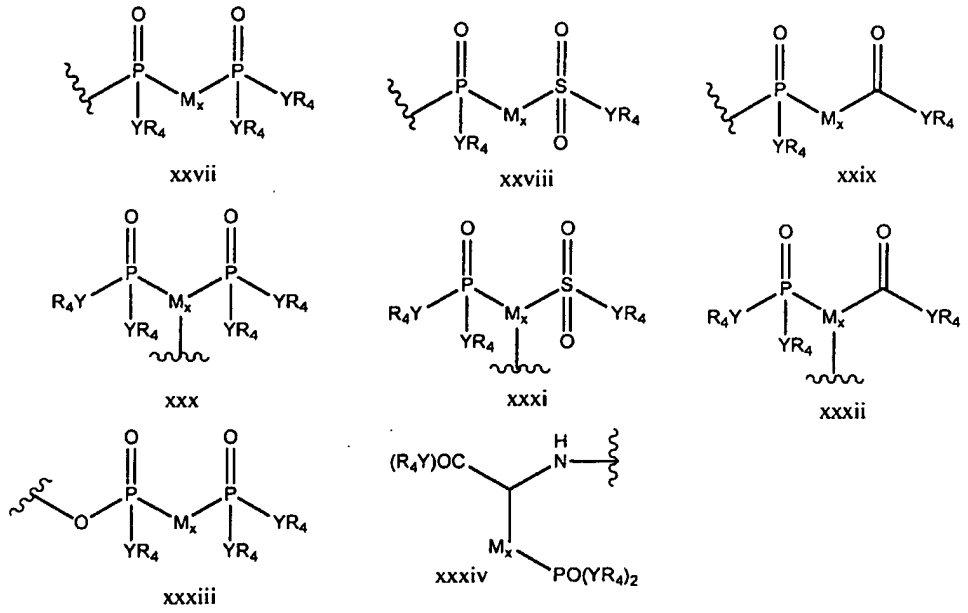
In certain embodiments, Tb is selected from x, xi, xii, xiii, xiv, xv, xxi, xxii, xxiii, xxiv, and xxv. In certain embodiments, Tb is selected from xi, xii, xiv, or xv. In certain embodiments, Tb is x. In certain embodiments, Tb is xiii. In certain embodiments, V represents NR_2. In certain embodiments, Tb is xxi, xxii, xxiii, xxiv, or xxv. In certain embodiments, Tb is xx.

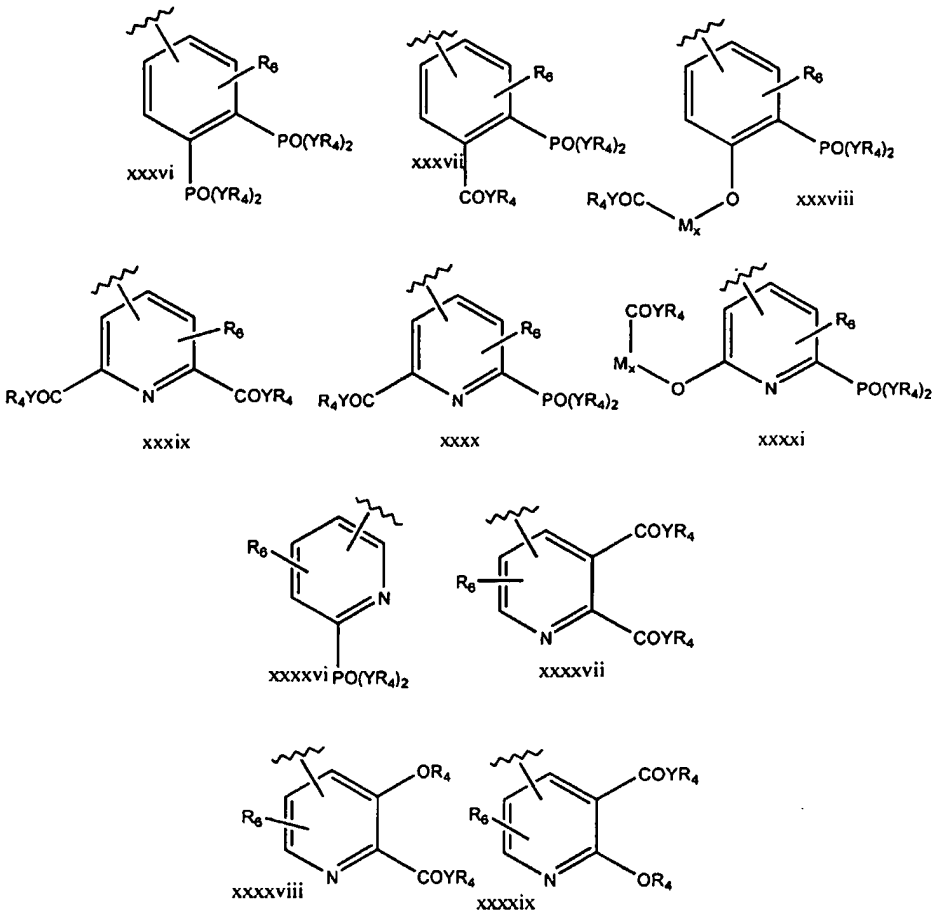
In certain embodiments, a subject compound has the structure of Formula VI: Tb-Cy-L-U, wherein Tb, Cy, L, and U are as defined above, and Tb is selected from i, ii, iii, iv, v, vi, vii, viii, and ix. In certain embodiments, Tb represents i, ii, iii, or iv, preferably i. In certain embodiments, Tb represents v or vi. In certain embodiments, Tb represents vii or viii. In certain embodiments, Tb represents ix. In certain embodiments, L is absent. In certain embodiments, Cy represents a phenyl ring.

In certain embodiments of Formulas I -VI, Tb represents:



In certain embodiments of Formulas I -VI, Tb may have a structure selected from:





wherein M is defined as above,

x represents 1,2, 3, 4, 5, or 6;

each occurence of Y is independently a covalent bond, -O-, -S-, or $-N(R_J)_2$, wherein R_J, for each occurence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

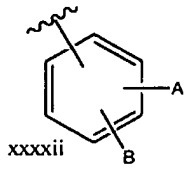
R_6 represents from 0-3 substituents selected from halogen, lower alkyl, lower alkenyl, aryl, heteroaryl, carbonyl, thiocarbonyl, ketone, aldehyde, amino, acylamino, amido, amidino, cyano, nitro, azido, sulfonyl, sulfoxido, sulfate, sulfonate, sulfamoyl, sulfonamido, phosphoryl, phosphonate, phosphinate, $-(CH_2)_p$alkyl, $-(CH_2)_p$alkenyl, $-(CH_2)_p$alkynyl, $-(CH_2)_p$aryl, $-(CH_2)_p$aralkyl, $-(CH_2)_pOH$, $-(CH_2)_pO$-lower alkyl, $-(CH_2)_pO$-lower alkenyl, $-O(CH_2)_nR$, $-(CH_2)_pSH$, $-(CH_2)_pS$-lower alkyl, $-(CH_2)_pS$-lower alkenyl, $-S(CH_2)_nR$, $-(CH_2)_pN(R)_2$, $-(CH_2)_pNR$-lower alkyl, $-(CH_2)_pNR$-lower alkenyl, $-NR_8(CH_2)_nR$, or protected forms of the above, and wherein p is 1-10; and

each occurrence of R_4 is independently hydrogen or a lower alkyl.

In certain embodiments, M, where it occurs in Tb is selected from CH_2, CHJ and CJ_2, wherein J represents a halogen, such as F, Cl, Br, or I, preferably F or Cl, even more preferably F.

In certain embodiments, R_6 is selected from lower alkyl, hydrophilic groups, and lower alkyl substituted with hydrophilic groups. Representative hydrophilic groups include hydroxyl, sulfhydryl, amino, amido, carboxyl, sulfonate, phosphonate, and salts thereof.

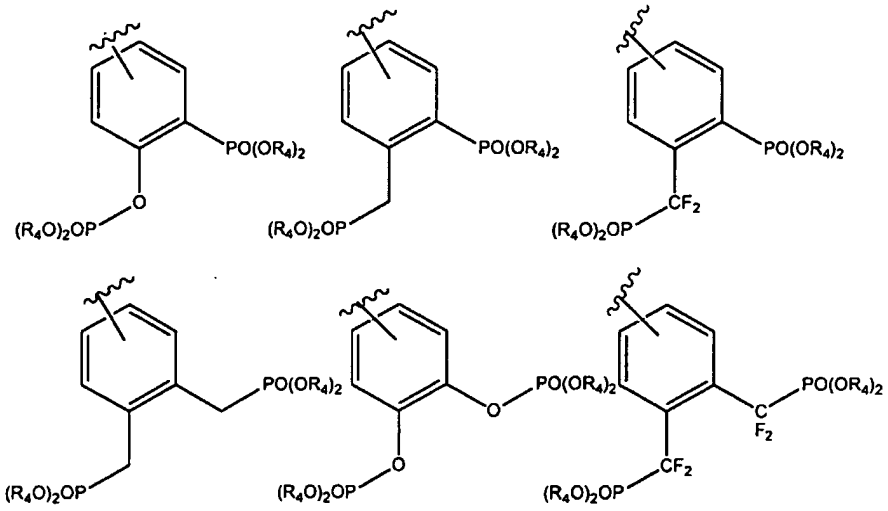
In certain embodiments of Formulas I -VI, Tb has the structure xxxxii:



xxxxii

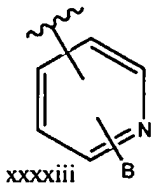
wherein A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms, such as CF_2, CH_2, O, S, NR, CH_2S, CH_2NR, CH_2O, etc.



In certain embodiments, the phenyl ring may bear one or more additional R_6 substituents. In certain embodiments, G is absent, while in other embodiments, G is present. In certain embodiments, at least one occurrence of G is absent. In certain embodiments, Tb has a structure such as:

In certain embodiments of Formulas I -VI, Tb has the structure xxxxiii:

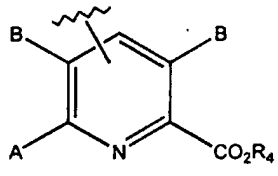


xxxxiii

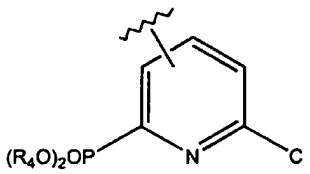
wherein B is defined as above.

In certain embodiments, the pyridyl ring may bear one or more additional R_6 substituents.

In certain embodiments of Formulas I -VI, Tb has the structure xxxxiv or xxxxv:



xxxxiv



xxxxv

wherein C represents H, R_6, NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, or GSO_3R_4, and in xxxxiv, any one occurrence of A or B is present, and the other occurrences may represent a bond to Z, H, or R_6 as desired.

In certain embodiments, the pyridyl ring may bear one or more additional R_6 substituents.

In certain embodiments of Formulas I -VI, Tb represents a heteroaryl, preferably a nitrogen-containing heteroaryl, bearing one B substituent, preferably an A substituent, or two B substituents, and optionally including one or more R_6 substituents. In preferred embodiments, the heteroaryl group is selected from thiazoline, oxazoline, pyrrole, pyrazole, imidazole, pyridine, pyrazine, pyridazine, and pyrimidine, preferably pyridine, pyrazole, pyrazine, and pyrimidine.

Solid Phase Synthesis and Combinatorial Libraries of Bone Targeting Agents

The inventive compounds may be prepared by any available method. Preferably, they are synthesized, for example using solution phase or solid phase techniques. Often, solid-phase syntheses will be modified versions of the compounds described herein that allow their attachment to a solid support. Thus, the present invention also contemplates particularly preferred because it enables the use of more rapid split and pool techniques to generate larger libraries (e.g., greater than 10,000 members) more easily. It will be appreciated that solid phase parallel synthesis techniques also can be utilized, such as those described in U.S. Patents 5,712,171 and 5,736,412, incorporated herein by reference.

A solid support, for the purposes of this invention, is defined as an insoluble material to which compounds are attached during a synthesis sequence. The use of a solid support is advantageous for the synthesis of libraries because the isolation of support-bound reaction products can be accomplished simply by washing away reagents from the support-bound material and therefore the reaction can be driven to completion by the use of excess reagents. Additionally, the use of a solid support also enables the use of specific encoding techniques to "track" the identity of the inventive compounds in the library. A solid support can be any material which is an insoluble matrix and can have a rigid or semi-rigid surface. Exemplary solid supports include, but are not limited to, pellets, disks, capillaries, hollow fibers, needles, pins, solid fibers, cellulose beads, pore-glass beads, silica gels, polystyrene beads optionally cross-linked with divinylbenzene, grafted co-poly beads, poly-acrylamide beads, latex beads, dimethylacrylamide beads optionally crosslinked with N-N'-bis-acryloylethylenediamine, and glass particles coated with a hydrophobic polymer. One of ordinary skill in the art will realize that the choice of particular solid support will be limited by the compatability of the support with the reaction chemistry being utilized. In one particularly preferred embodiment, a Tentagel amino resin, a composite of 1) a polystyrene bead crosslinked with divinylbenzene and 2) PEG (polyethylene glycol), is employed for use in the present invention. Tentagel is a particularly useful solid support because it provides a versatile support for use in on-bead or off-bead assays, and it also undergoes excellent swelling in solvents ranging from toluene to water.

The compounds of the present invention may be attached directly to the solid support or may be attached to the solid support through a linking reagent. Direct attachment to the solid support may be useful if it is desired not to detach the library member from the solid support. For example, for direct on-bead analysis of biological/pharmacological activitiy or analysis of the compound structure, a stronger interaction between the library member and the solid support may be desirable. Alternatively, the use of a linking reagent may be useful if more facile cleavage of the inventive library members from the solid support is desired.

Furthermore, any linking reagent used in the present invention may comprise a single linking molecule, or alternatively may comprise a linking molecule and one or more spacer molecules. A spacer molecule is particularly useful when the particular reaction conditions require that the linking molecule be separated from the library member, or if additional distance between the solid support/linking unit and the library member is desired. In one particularly preferred embodiment, photocleavable linkers are employed to attach the solid phase resin to the component. Photocleavable linkers are particularly advantageous for the presently claimed invention because of the ability to use these linkers in in vivo screening strategies. Once the inventive compound is released from the solid support via photocleavage, the compound is able to enter the cell. Exemplary photocleavable linkers include, but are not limited to ortho-Nitrobenzyl photolinkers and dithiane protected benzoin photolinkers. One of ordinary skill in the art will readily appreciate that the method of the present invention is not limited to the use of photocleavable linkers; rather other linkers may be employed, preferably those that are capable of delivering the desired compounds in vivo.

In one embodiment of the present invention, the synthesis of libraries of bone targeting agents is performed using established combinatorial methods for solution phase, solid phase, or a combination of solution phase and solid phase synthesis techniques. The synthesis of combinatorial libraries is well known in the art and has been reviewed (see, e.g., "Combinatorial Chemistry", Chemical and Engineering News, Feb. 24, 1997, p. 43; Thompson, L.A., Ellman, J.A., *Chem. Rev.* **1996**, *96*, 555, incorporated herein by reference.) One of ordinary skill in the art will realize that the choice of method will depend upon the specific number of compounds to be

synthesized, the specific reaction chemistry, and the availability of specific instrumentation, such as robotic instrumentation for the preparation and analysis of the inventive libraries. In particularly preferred embodiments, the reactions to be performed on the inventive scaffolds to generate the libraries are selected for their ability to proceed in high yield, and in a stereoselective fashion, if applicable.

In one embodiment of the present invention, libraries are generated using a solution phase technique. Traditional advantages of solution phase techniques for the synthesis of combinatorial libraries include the availability of a much wider range of organic reactions, and the relative ease with which products can be characterized.

In a preferred embodiment, for the generation of a solution phase combinatorial library, a parallel synthesis technique is utilized, in which all of the products are assembled separately in their own reaction vessels. In a particularly preferred parallel synthesis procedure, a microtitre plate containing n rows and m columns of tiny wells which are capable of holding a few milliliters of the solvent in which the reaction will occur, is utilized. It is possible to then use n variants of reactant A, and m variants of reactant B, to obtain n x m variants, in n x m wells. One of ordinary skill in the art will realize that this particular procedure is most useful when smaller libraries are desired, and the specific wells can provide a ready means to identify the library members in a particular well.

In another embodiment of the present invention, a solid phase synthesis technique is utilized, in which the desired scaffold structures are attached to the solid phase directly or though a linking unit, as discussed above. Advantages of solid phase techniques include the ability to more easily conduct multi-step reactions and the ability to drive reactions to completion because excess reagents can be utilized and the unreacted reagent washed away. Perhaps one of the most significant advantages of solid phase synthesis is the ability to use a technique called "split and pool", in addition to the parallel synthesis technique, develped by Furka. (Furka et al., *Abstr. 14th Int. Congr. Biochem.*, Prague, Czechoslovakia, **1988**, *5*, 47; Furka et al., *Int. J. Pept. Protein Res.* **1991**, *37*, 487; Sebestyen et al., *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 413) In this technique, a mixture of related compounds can be made in the same reaction vessel, thus substantially reducing the number of containers required for the synthesis of very large libraries, such as those containing as many as or more than one

million library members. As an example, the solid support scaffolds can be divided into n vessels, where n represents the number species of reagent A to be reacted with the scaffold structures. After reaction, the contents from n vessels are combined and then split into m vessels, where m represents the number of species of reagent B to be reacted with the scaffold structures. This procedure is repeated until the desired number of reagents is reacted with the scaffold structures to yield the inventive library.

The use of solid phase techniques in the present invention may also include the use of a specific encoding technique. Specific encoding techniques have been reviewed by Czarnik. (Czarnik, A.W., *Current Opinion in Chemical Biology*, **1997**, *1*, 60) As used in the present invention, an encoding technique involves the use of a particular "identifiying agent" attached to the solid support, which enables the determination of the structure of a specific library member without reference to its spatial coordinates. One of ordinary skill in the art will also realize that if smaller solid phase libraries are generated in specific reaction wells, such as 96 well plates, or on plastic pins, the reaction history of these library members may also be identified by their spatial coordinates in the particular plate, and thus are spatially encoded. It is most preferred, however for large combinatorial libraries, to use an alternative encoding technique to record the specific reaction history.

Examples of alternative encoding techniques that can be utilized in the present invention include, but are not limited to, spatial encoding techniques, graphical encoding techniques, including the "tea bag" method, chemical encoding methods, and spectrophotometric encoding methods. Spatial encoding refers to recording a reaction's history based on its location. Graphical encoding techniques involve the coding of each synthesis platform to permit the generation of a relational database. Examples of preferred spectrophotometic encoding methods include the use of mass spectroscopy, fluorescence emission, and nuclear magnetic resonance spectroscopy. In a preferred embodiment, chemical encoding methods are utilized, which uses the structure of the reaction product to code for its identity. Decoding using this method can be performed on the solid phase or off of the solid phase. One of ordinary skill in the art will realize that the particular encoding method to be used in the present

invention must be selected based upon the number of library members desired, and the reaction chemistry employed.

Subsequent characterization of the library members, or individual compounds, can be performed using standard analytical techniques, such as mass spectrometry, Nuclear Magnetic Resonance Spectroscopy, and gas chromatrography.

Once specific libraries of compounds have been prepared, specific assay techniques, such as those described herein, may be utilized to test the ability of compounds to function as Src kinase inhibitors. In certain preferred embodiments, high throughput assay techniques are utilized.

Uses of Compounds of the Invention

As discussed above, the compounds of the present invention are useful in the selective treatment or prevention of bone disorders. These compounds or pharmaceutical compositions may effect treatment via inhibition of osteoclast activity, promotion of osteoblast activity, or promotion or inhibition of other cellular events necessary for healthy bone metabolism. In certain preferred embodiments, these compounds are useful for the treatment or prevention of diseases and conditions associated with bone metabolic disorders such as osteoclast overactivity. In still other preferred embodiments, the compounds of the present invention are targeted Src kinase inhibitors and thus inhibit bone resorption by osteoclasts.

The present invention therefore provides a method for the treatment, prophylaxis, and/or prevention of bone and other related disorders which method comprises the administration of an effective non-toxic amount of an inventive compound, or a pharmaceutically composition thereof. As mentioned above, although the inventive compounds effect treatment via several mechanisms, (i.e. inhibition of osteoclast activity, promotion of osteoblast activity, or regulation of other cellular events necessary for healthy bone metabolism), in certain preferred embodiments, these compounds are selective inhibitors of osteoclast activity.

In a further aspect, the present invention provides an inhibitor of mammalian osteoclasts, for example any one of the compounds of the present invention or a pharmaceutical composition thereof. In still another aspect, the present invention provides compounds or pharmaceutical compositions that are selective Src kinase

inhibitors. In particular, the method of present invention comprises providing any one of the compounds of the present invention or a pharmaceutically composition thereof, for use in the treatment of and/or prophylaxis of osteoporosis and related osteopenic diseases.

It will also be appreciated that, although many of the compounds and compositions described herein comprise a bone targeting moiety and a payload, the present invention also contemplates the use of bone targeting agents alone for the treatment of bone disorders, preferably by the selective inhibition of osteoclast activity.

It will further be appreciated that, in addition to the treatment or prevention of osteoporosis, particularly osteoporosis associated with the peri and post menopausal conditions, the present invention also contemplates the treatment and prophylaxis or prevention of Paget's disease, hypercalcemia associated with bone neoplasms and other types of osteoporotic diseases and related disorders, including but not limited to involutional osteoporosis, Type I or postmenopausal osteoporosis, Type II or senile osteoporosis, juvenile osteoporosis, idiopathic osteoporosis, endocrine abnormality, hyperthyroidism, hypogonadism, ovarian agensis or Turner's syndrome, hyperadrenocorticism or Cushing's syndrome, hyperparathyroidism, bone marrow abnormalities, multiple myeloma and related disorders, systemic mastocytosis, disseminated carcinoma, Gaucher's disease, connective tissue abnormalities, osteogenesis imperfecta, homocystinuria, Ehlers-Danlos syndrome, Marfan's syndrome, Menke's syndrome, immobilization or weightlessness, Sudeck's atrophy, chronic obstructive pulmonary disease, chronic heparin administration, and chronic ingestion of anticonvulsant drugs

In addition to providing compounds for the selective inhibition of Src tyrosine kinase (and thus the inhibition of osteoclast activity), the present invention contemplates the use of alternate payloads to achieve desired therapeutic effects. The targeted constructs of the present invention may include any of a wide variety of chemical entities to be delivered to the target site or into target cells. Generally, the payloads may be categorized as therapeutic agents (such as Src kinase inhibitors) or imaging agents. Imaging agents comprise those payloads which are detectable, e.g., by emitting light, radioactive emissions, or chemical signals, by absorbing radiation

(e.g., x-rays), or by otherwise changing a characteristic of treated cells relative to untreated cells. Therapeutic agents include payloads which are biologically active, preferably by countering an abnormal condition of the bone targeted site (e.g., tumor or infection).

A therapeutic agent useful in a targeted compound may be any of a number of chemical entities, e.g., an enzyme, drug, radionuclide, enzyme inhibitor, etc. For example, moieties useful as therapeutic agents include inhibitors of osteoclast activity such as Src kinase inhibitors, cathespin inhibitors, or proton pump inhibitors, amino acids and their derivatives; analgesics such as acetaminophen, aspirin, and ibuprofen; antifungal agents including: allyamines, imidazoles, polyenes, and triazoles; antigens and antibodies thereto; antihistamines such as chlorpheniramine and brompheniramine; antihypertensive agents such as clonidine, methyldopa, prazosin, verapamil, nifedipine, captopril, and enalapril; antiinflammatory agents including non-steroidal agents, such as aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives thiazinecarboxamides and others, as well as steroidal agents, such as glucocorticoids; antimicrobials such as aminoglycosides, amphenicols, cinoxacin, ciprofloxacin, 2,4-diaminopyrimidines, β-lactams (e.g., carbapenems, cephalosporins, cephamycins, monobactams, oxacephems and penicillins), lincosamides, macrolides, nitrofurans, norfloxacin, peptides, polypeptides, and proteins (e.g., defensins, bacitracin, polymyxin, cecropins, magainin II, indolicidin, ranalexin, protegrins, gallinacins, tritrpticin, lactoferricin, drosomycin, holotricin, thanatin, dermaseptin, iturins, syringomycins, nikkomycins, polyoxins, FR-900403, echinocandins, pneumocandins, aculeacins, mulundocandins, WF11899, aureobasidins, schizotrin A, cepacidines, zeamatin, cyclopeptides and D4e1), quinolones and analogs, sulfonamides, sulfones, tetracyclines; apoproteins, antivirals including: purines/pyrimidinones (e.g. acyclovir, dideoxy -cytidine, -adenosine, or -inosine, interferons, amantadine, ribavirin); beta-blockers such as propranolol, metoprolol, atenolol, labetolol, timolol, penbutolol, and pindolol; cancer drugs including chemotherapeutic agents; cardiovascular agents including cardiac glycosides, antianginals and vasodilators; coenzymes; enzymes; enzyme inhibitors; expectorants; glycoproteins; H-2 antagonists such as nizatidine, cimetidine,

famotidine, and ranitidine; haptens and antibodies thereto; hormones, lipids, liposomes; protein analogs in which at least one non-peptide linkage replaces a peptide linkage; phospholipids; prostaglandins; radionuclides (e.g. ^{131}I, ^{186}Re, ^{188}Re, ^{90}Y, ^{212}Bi, ^{211}At, ^{89}Sr, ^{166}Ho, ^{153}Sm, ^{67}Cu and ^{64}Cu); receptors and other membrane proteins; retro-inverso oligopeptides; stimulants; toxins such as aflatoxin, digoxin, rubratoxin, and xanthotoxin; tranquilizers such as diazepam, chordiazepoxide, oxazepam, alprazolam, and triazolam; and vitamins and mineral and nutritional additives. For other therapeutic agents, see, e.g., the Merck Index. The present invention contemplates agents that are useful for treating or preventing the progression of a bone or other related disorder, preferably by inhibiting osteoclast activity.

In an exemplary embodiment, the compounds and compositions of the present invention are also inhibitors of cathepsin K, and thus can be used to treat bone disorders. In particular, it has been discovered that osteoclasts contain large quantities of cathepsin K and it has been suggested that cathepsin K thus plays an important role in bone resorption (Smith et al., *Exp. Opin. Ther. Patents* **1999**, *9*, 683-694 and references cited therein). For example, it has been reported that the enzyme is active over a pH range (3.5-4.0) consistent with the pH of the local bone environment during resorption, that a cathepsin K antisense nucleotide was effective in the inhibition of osteoclast bone resorption, and that there is a link between mutations in the human cathepsin K gene and the rare skeletal dysplasia, pycnodysostosis, a disease characterized by abnormal bone resorption (see, Smith et al.). Thus compounds of the present that are cathepsin K inhibitors would be useful as agents for the inhibition of bone resorption and thus could be used to treat osteoporosis or other disorders resulting from abnormal bone resorption.

Bone-targeted compounds can alternatively or additionally be labeled with any of a variety of imaging agents which are known in the art and which will depend to some extent on the means used to detect or monitor the compound *in vivo* or *in vitro*. Preferred imaging agents for performing positron emission tomography (PET) and single photon emission computer tomography (SPECT) include F-18, Tc-99m, and I-123. Preferred imaging agents for magnetic resonance imaging (MRI) include an appropriate atom with unpaired spin electrons or a free radical.

When the payload is intended to perform in an imaging capacity, the payload comprises a moiety such as a radionuclide or paramagnetic contrast agent, fluorescent or chemiluminescent label, or other type of detectable marker. The imaging agents described above may contain any label in accordance with the invention. Highly specific and sensitive labels are provided by radionuclides, which can then be detected using positron emission tomography (PET) or Single Photon Emission Computed Tomography (SPECT) imaging. More preferably, the imaging agent of the invention contains a radionuclide selected from the group consisting of ^{131}I, ^{125}I, ^{123}I, ^{99m}Tc, ^{18}F, ^{68}Ga, ^{67}Ga, ^{72}As, ^{89}Zr, ^{64}Cu, ^{62}Cu, ^{111}In, ^{203}Pb, ^{198}Hg, ^{11}C, ^{97}Ru, and ^{201}Tl or a paramagnetic contrast agent, such as gadolinium, cobalt, nickel, manganese, and iron. As will be appreciated, these atoms may be directly incorporated into the bone targeting moiety or the payload.

Therapeutic/Prophylactic Administration and Pharmceutical Compositions

As discussed above, the compounds of the present invention are useful in the treatment of bone disorders, preferably imbalances in bone metabolism, such as overactivity of bone resorption. In certain preferred embodiments, the compounds of the present invention are useful as inhibitors of Src tyrosine phosphorylation.

When the compounds of the present invention are used for therapeutic and/or prophylactic administration, they can exist in free form, or, where appropriate, in salt form. Pharmceutically acceptable salts of many types of compounds and their preparation are well-known to those of skill in the art. The pharmaceutically acceptable salts of compounds of this invention include the conventional non-toxic salts or the quaternary ammonium salts of such compounds which are formed, for example, from inorganic or organic acids of bases.

The compounds of the invention may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in solution with an appropriate organic solvent.

This invention relates to pharmaceutical compositions comprising a therapeutically (or prophylactically) effective amount of the compound, and a pharmaceutically acceptable carrier or excipient. Carriers include, e.g., saline,

buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof, and are discussed in greater detail below. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release forrmulation, or powder. The compsition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Formulation may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier may be, for example, either a solid or liquid.

Illustrative solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidannts, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Illustrative liquid carriers include syrup, peanut oil, olive oil, water, et. Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring aents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above,

e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carders are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically propellant. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compound can also be administered orally either in liquid or solid composition form.

The carrier or excipient may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate along or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like. When formulated for oral administration, 0.01% Tween 80 in PHOSAL PG-50 (phospholipid concentrate with 1,2-propylene glycol, A. Nattermann & Cie. GmbH) has been recognized as providing an acceptable oral formulation for other compounds, and may be adapted to formulations for various compounds of this invention.

A wide variety of pharmaceutical forms can be employed. If a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1g. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectible solution or suspension in an ampule or vial or nonaqueous liquid suspension.

To obtain a stable water soluble dosage form, a pharmaceutically acceptable salt of the compound may be dissolved in an aqueous solution or an organic or inorganic acid, such as a 0.3 M solution of succinic acid or citric acid. Alternatively, acidic derivatives can be dissolved in suitable basic solutions. If a soluble salt form is not available, the compound is dissolved in a suitable cosolvent or combinations thereof. Examples of such suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin, polyoxyethylated

fatty acids, fatty alcohols or glycerin hydroxy fatty acids esters and the like in concentrations ranging from 0-60% of the total volume.

Various delivery systems are know and can be used to administer the compound, or the various formulations thereof, including tablets, capsules, injectable solutions, encapsulation in liposomes, microparticles, microcapsules, etc. Methods of introduction include but are not limited to dermal, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, pulmonary, epidural, ocular and (as is usually preferred) oral routes. The compound may be administered by any convenient or otherwise appropriate route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g. oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. For treatment or prophylaxis of nasal, bronchial or pulmonary conditions, preferred routes are oral, nasal or via a bronchial aerosol or nebulizer.

In certain embodiments, it may desirable to administer the compound locally to an area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, by injection, by means of a catheter, by means of a suppository, or by means of a skin patch or implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the side of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantitity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by

injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

Administration to an individual of an effective amount of the compound can also be accomplished topically by administering the compound(s) directly to the affected area of the skin of the individual. For this purpose, the compound is administered or applied in a composition including a pharmacologically acceptable carrier, such as a gel, an ointment, a lotion, or a cream, which includes, without limitation, such carriers as water, glycerol, alcohol, propylene glycol, fatty acids, triglycerides, fatty acid esters, or mineral oils.

Other topical carriers include liquid petroleum, isopropyl palmitate, polyethylene glycol, ethanol (95%), polyoxyethylene monolaurate (5%) in water, or sodium lauryl sulfate (5%) in water. Other materials such as anti-oxidants, humectants, viscosity stabilizers, and similar agents may be added as necessary. Percutaneous penetration enhancers such as Azone may also be included.

In addition, in certain instances, it is expected that the compound may be disposed witin devices placed upon, in, or under the skin. Such devices include patches, implants, and injections which release the compound into the skin, by either passive or active release mechanisms.

Materials and methods for producing the various formaulations are well known in the art and may be adapted for practicing the subject invention. See e.g. US Patent Nos. 5,182,293 and 4,837,311 (tablets, capsules and other formulations as well as intravenous formulations) and European Patent Application Publication Nos. 0 649 659 (published April 6, 1995; illustrative formulation for IV administration) and 0 648 494 (published April 19, 1995; illustrative formulation for oral administration).

The effective dose of the compound will typically be in the range of about 0.01 to about 50 mg/kgs, preferably about 0.1 to about 10 mg/kg of mammalian body weight, administered in single or multiple doses. Generally, the compound may be administered to patients in need of such treatment in a daily dose range of about 1 to about 2000 mg per patient.

The amount of compound which will be effective in the treatment or prevention of a particular disorder or condition will depend in part on the nature and severisty of the disorder or condition, which can be determined by standard clinical

techniques. In addition, in vitro or in vivo assays may optionally be employed to help identify optimal dose ranges. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. The precise dosage level should be determined by the attending physician or other health care provider and will depend upon well known factors, including route of administration, and the age, body weight, sex and general health of the individual; the nature, severity and clinical stage of the disease; the use (or not) of concomitant therapies.

Treatment Kits

In other embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. In general, the pharmaceutical pack or kit comprises one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages, and may also include a card having the dosages oriented in the order of their intended use. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium dietary supplements, either in a form similar to or distinct from the bone targeted dosages, can be included to provide a kit in which a dosage is taken every day. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Equivalents

The representative examples which follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including

the examples which follow and the references to the scientific and patent literature cited herein. It should further be appreciated that the contents of those cited references are incorporated herein by reference to help illustrate the state of the art.

The following examples contain important additional information, exemplification and guidance which can be adapted to the practice of this invention in its various embodiments and the equivalents thereof.

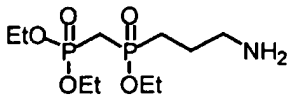
Exemplification

The described phosphorus-containing moieties can be synthesized according to the schemes outlined below:

A) Embodiments wherein Tb is i

Example 1

[(3-Amino-propyl)-ethoxy-phosphinoylmethyl]-phosphonic acid diethyl ester



[(3-Benzyloxy-propyl)-ethoxy-phosphinoylmethyl]-phosphonic acid diethyl ester:
To an oven-dried flask was added 10.25 g (44.7 mmol) of (3-Bromo-propoxymethyl)-benzene and 7.67 mL (44.7mmol) of triethyl phosphite. The flask was fitted with a short-path distillation head, for removal of bromoethane, and the mixture heated at 150 °C for 4 h. The reaction was cooled to ambient temperature, and then diluted with 120 mL of absolute ethanol and 1.8 N KOH (120mL, 216 mol). The distillation head was replaced with a reflux condenser and the solution heated at reflux for 5 h. The reaction was cooled then concentrated *in vacuo*. The basic aqueous layer was extracted with EtOAc (2x) and then acidified to pH 3 with conc. HCl. The aqueous layer was extracted with EtOAc (3x) and the combined extracts were dried over $MgSO_4$ and concentrated. The resulting crude product (8.24 g) was used as is in the next reaction. ^{31}P NMR (300 MHz, DMSO-d_6) δ 34.113.

To a solution of the crude phosphonate (8.24 g, 32.5 mmol) in 100 mL CH_2Cl_2, under an atmosphere of N_2, was added 10.8 mL (113.8 mmol) of oxalyl chloride. DMF (several drops) was slowly added to initiate the reaction. After gas

evolution had ceased, the reaction was stirred for 30 min at ambient temperature. Upon concentration *in vacuo*, the residue was titurated several times with hexane, then dissolved in 167 mL of anhydrous THF. In a separate flask, a cooled (-78 °C, under N_2) solution of diethyl methylphosphonate (10.25 mL, 69.9 mmol) in 337 mL of anhydrous THF was added 2.5 M n-butyl lithium (27.95 mL, 69.9 mmol) dropwise. The reaction mixture was stirred for 30 min at -78 °C, at which time the *in situ* generated acid chloride was added dropwise. The solution was stirred for an additional 2.5 h at -78 °C, quenched with 5 mL glacial acetic acid, and then warmed to ambient temperature. Water was added to the reaction mixture and the THF was removed *in vacuo*. The aqueous layer was extracted with EtOAc (3x) and the combined organics washed with saturated $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (eluted with 50:1 CH_2Cl_2/MeOH) affording 6.15 g of a yellow oil. ^{31}P NMR (300 MHz, DMSO-d_6) δ 51.479, 26.291.

[(3-Amino-propyl)-ethoxy-phosphinoylmethyl]-phosphonic acid diethyl ester:

To a solution of [(3-Benzyloxy-propyl)-ethoxy-phosphinoylmethyl]-phosphonic acid diethyl ester (5.7 g, 14.5 mmol) in 100 mL of EtOH was added 1.2 g of palladium on carbon. The mixture was flushed with H_2 and stirred at ambient temperature (H_2 balloon) for 1 h. The reaction mixture was filtered through Celite and the solvent evaporated to provide 3.5 g of a pale yellow oil. ^{31}P NMR (300 MHz, DMSO-d_6) d 52.219, 26.317.

To a cooled (0 °C, under N_2) solution of the crude alcohol (3.5 g, 14.5 mmol) in 53 mL of CH_2Cl_2 was added 2.4 mL (17.4 mmol) of triethylamine followed by 1.25 mL (16 mmol) of methanesulfonyl chloride. The reaction mixture was warmed to ambient temperature and stirred for 1 h. The reaction mixture was then quenched with water and the layers separated. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The crude orange-yellow oil (5.5 g) was used as is in the next reaction. ^{31}P NMR (300 MHz, DMSO-d_6) δ 51.135, 26.614.

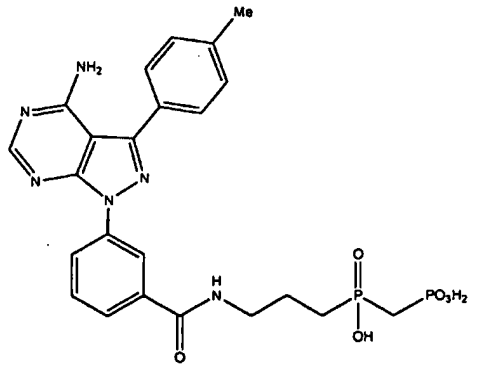
To a solution of the crude mesylate (5.5 g, 14.4 mmol) in 17 mL DMF was added 4.7 g (72.4 mmol) of sodium azide. The resulting slurry was heated at 55 °C and stirred overnight. The reaction mixture was diluted with EtOAc and washed with

water (2x). The combined organics were then dried over Na_2SO_4 and concentrated. The crude azide (2.61 g) was used as is in the next reaction. ^{31}P NMR (300 MHz, DMSO-d_6) d 51.230, 26.183.

To a solution of the crude azide (2.61 g, 8 mmol) in 100 mL of EtOH was added 0.8 g of palladium on carbon. The mixture was flushed with H_2 and stirred at ambient temperature (H_2 balloon) for 16 h. The reaction mixture was filtered through Celite and the solvent evaporated to provide 2.3 g of a yellow oil: ^1H NMR (300 MHz, DMSO-d_6) δ 4.03 (m, 6H), 2.84-2.52 (m, 4H), 1.91-1.80 (m, 2H), 1.65-1.61 (m, 2H), 1.23 (m,9H). ^{31}P NMR (300 MHz, DMSO-d_6) δ 51.757, 26.344.

Example 2

({3-[3-(4-Amino-3-*p*-tolyl-pyrazolo[3,4-*d*]pyrimidin-1-yl)-benzoylamino]-propyl}-hydroxy-phosphinoylmethyl)-phosphonic acid



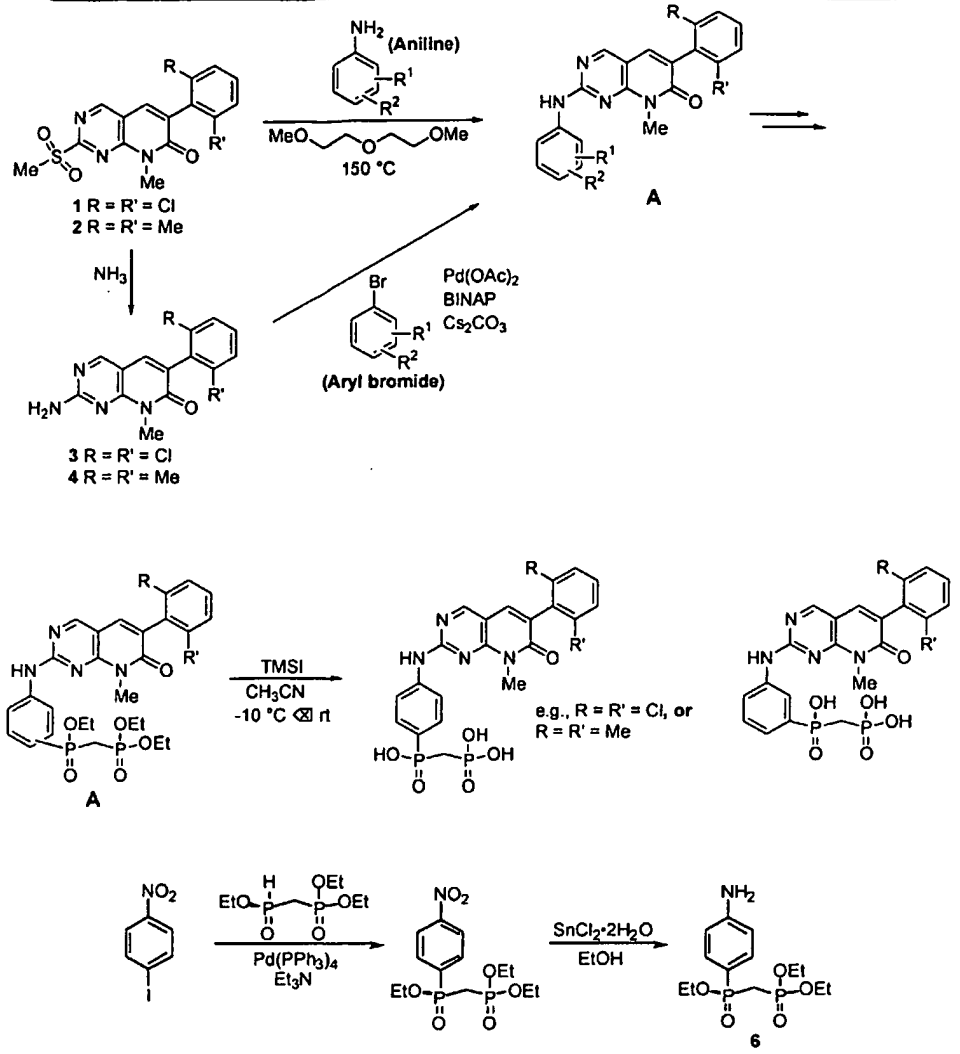
The title compound was made as for example 16 (below) using [(3-amino-propyl)-ethoxy-phosphinoylmethyl]-phosphonic acid diethyl ester.

Example 3

Synthesis of Phenyl-*i* compounds

For the synthesis of these examples, one of two coupling procedures can be used, either the coupling of sulfone **1/2** with the aniline or the coupling of amine **3/4** with the aryl bromide.

General Scheme for Targeted Aminopyrido[2,3-*d*]pyrimidin-7(8*H*)-ones

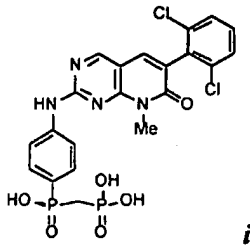


Synthesis of aniline 6

(a) A mixture of diethyl (ethoxyphosphinyl)methylphosphonate (2.35 g, 9.62 mmol), Et_3N (3.8 mL, 27.5 mmol), 1-iodo-4-nitrobenzene (2.28 g, 9.17 mmol) and $Pd(PPh_3)_4$ (265 mg, 0.229 mmol) in CH_3CN (14 mL) under N_2 was stirred at 80 °C for 2.5 h. After cooling to rt, the reaction mixture was poured into 50 mL of 1 *N* aq HCl and extracted with CH_2Cl_2. The extract was washed with H_2O (50 mL) and brine (50 mL). The aqueous washes were reextracted once with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 30:1 $CHCl_3$-MeOH

followed by 20:1 $CHCl_3$-MeOH and finally 15:1 $CHCl_3$-MeOH afforded 3.28 g (98%) of the desired (arylphosphinylmethyl)phosphonate.

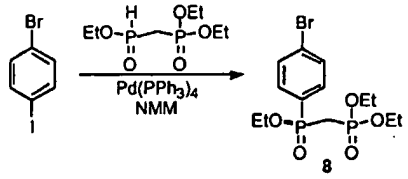
(b) A mixture of the nitroarene (940 mg, 2.57 mmol) and $SnCl_2 \cdot 2H_2O$ (2.9 g, 12.9 mmol) in EtOH (~10 mL) was stirred at 70 °C for 44 min and then concentrated at rt. The residue was taken up in CH_2Cl_2 and washed with half saturated aq $NaHCO_3$ (40 mL), H_2O (40 mL) and brine (40 mL). The aqueous washes were reextracted once with CH_2Cl_2, and the combined extracts were dried over K_2CO_3 and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 20:1 $CHCl_3$-MeOH followed by 15:1 $CHCl_3$-MeOH afforded 657 mg (76%) of aniline **6**.



i-A

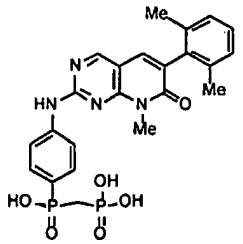
(a) A mixture of aniline **6** (1.89 g, 5.65 mmol) and sulfone **1** (866 mg, 2.25 mmol) in 2-methoxyethyl ether (3 mL) was stirred at 150 °C for 6 h. The reaction mixture was allowed to cool to rt. It was then diluted with a small amount of $CHCl_3$ and purified by flash chromatography on silica gel. Elution with 30:1 $CHCl_3$-MeOH, 20:1 1 $CHCl_3$-MeOH, and 15:1 1 $CHCl_3$-MeOH afforded material that was still very impure. The chromatography was repeated using the same eluants to provide material that was still fairly impure. This material was then purified by reversed phase HPLC using water-acetonitrile (+0.1% TFA). The fractions containing product were collected and concentrated to a small volume (~20 mL). The residue was then partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was reextracted twice with CH_2Cl_2. The combined extracts were dried over K_2CO_3 and concentrated to 429 mg (30%) of pure coupled product.

(b) To a solution of the coupled product (420 mg, 0.657 mmol) in 10 mL of CH_3CN at -10 °C was added TMSI (1.40 mL, 9.85 mmol). The reaction mixture was stirred at -10 °C for 15 min. and at rt for 75 min. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$ (~13 mL), a few drops of aqueous $NaHSO_3$ and H_2O (~2 mL). The mixture was further diluted with a small amount of DMF and then purified by reversed phase HPLC using water-acetonitrile (+0.1% TFA). The fractions containing product were then lyophilized to afford pure ***i*-A**.



Synthesis of aryl bromide 8

A mixture of diethyl (ethoxyphosphinyl)methylphosphonate (1.85 g, 7.58 mmol), 1-bromo-4-iodobenzene (1.95 g, 6.89 mmol), NMM (1.51 mL, 13.8 mmol) and $Pd(PPh_3)_4$ (199 mg, 0.172 mmol) in CH_3CN was stirred at 100 °C overnight. After cooling to rt, the reaction mixture was concentrated. The residue was then partitioned between 1 *N* aq HCl and CH_2Cl_2. The layers were separated, and the organic layer was washed with H_2O and brine. The aqueous washes were reextracted once with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 30:1 $CHCl_3$-MeOH followed by 20:1 $CHCl_3$-MeOH and finally 15:1 $CHCl_3$-MeOH afforded 1.52 g (55%) of aryl bromide **8** contaminated with a trace amount of Ph_3PO.

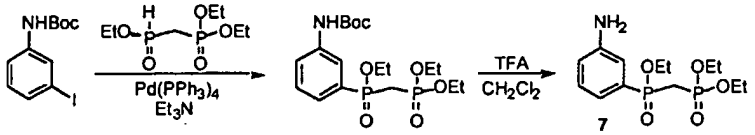


***i*-B**

(a) Into a glass pressure tube containing sulfone **2** (235 mg, 0.684 mmol) at -78 °C was condensed NH_3 (~2 mL). The tube was capped and allowed to warm to rt. The reaction mixture was allowed to stir at rt overnight, and then the NH_3 was allowed to evaporate. The residue was purified by flash chromatography on silica gel. Elution with 40:1 $CHCl_3$-MeOH afforded 193 mg (quant) of amine **4**.

(b) A mixture of amine **4** (176 mg, 0.628 mmol), aryl bromide **8** (301 mg, 0.753 mmol), powdered Cs_2CO_3 (368 mg, 1.13 mmol), BINAP (59 mg, 0.0942 mmol) and $Pd(OAc)_2$ (14 mg, 0.0.0628) in toluene (3.5 mL) was stirred at 100 °C overnight. After cooling, the reaction mixture was partitioned between CH_2Cl_2 and 1 *N* aq HCl. The layers were separated, and the organic layer was washed with H_2O and brine. The aqueous washes were reextracted once with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 30:1 $CHCl_3$-MeOH followed by 20:1 $CHCl_3$-MeOH and finally 15:1 $CHCl_3$-MeOH afforded 231 mg (62%) of the desired coupled product.

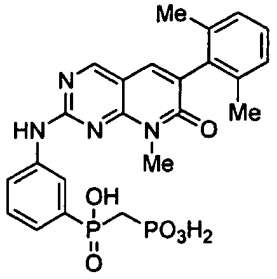
(c) The coupled product was then converted to ***i*-B** in the same fashion as previously described (***i*-A, (b)**).



Synthesis of aniline 7

(a) The intermediate (arylphosphinyl)methylphosphonate was prepared from *N*-(*t*-butylcarbonyl)-3-iodoaniline in a manner analogous to that described for the synthesis of aryl bromide **8**.

(b) The intermediate carbamate was converted to aniline **7** in a manner analogous to that described for **5 (f)**.



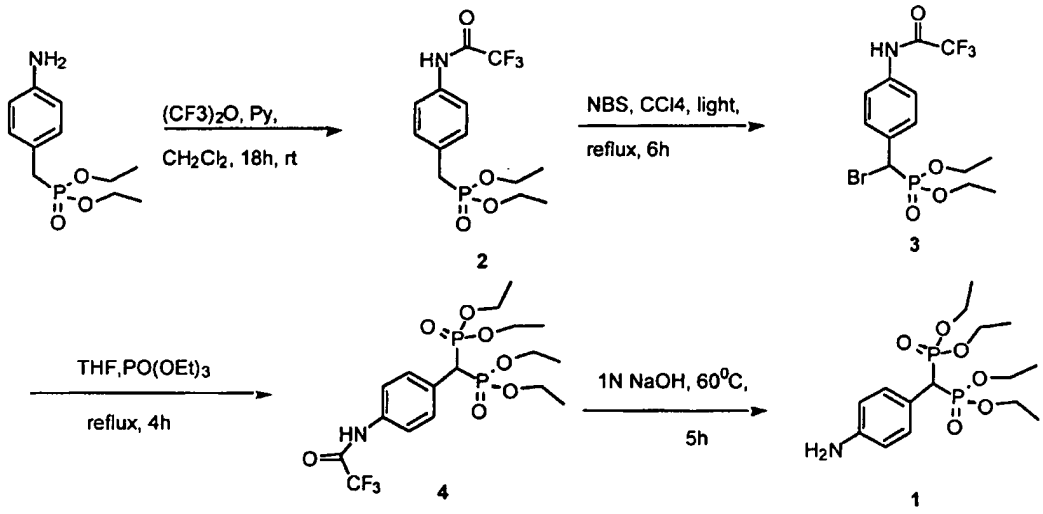
i-C

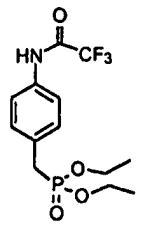
(a) Aniline **7** was condensed with sulfone **1** in a manner analogous to the condensation of aniline **6** with sulfone **1** (***i*-A, (a)**).

(b) The coupled product was then converted to ***i*-C** in the same fashion as previously described (***i*-A, (b)**).

B) Embodiments wherein Tb is vi

A bone-targeting group vi was synthesized according to the following scheme:

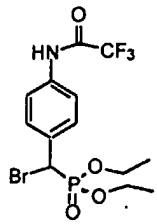




2

Diethyl (4-(N-trifluoroacetyl amino benzyl) phosphonate 2:

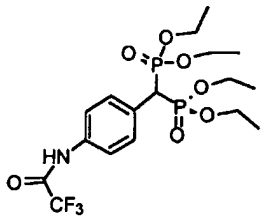
To diethyl (4-aminobenzyl)phosphonate (10 g) in anhydrous dichloromethane (100 mL) was added pyridine (4.0 mL)followed by trifluoroacetic anhydride (7.0 mL) and stirred at rt overnight (~18 hrs). Reaction mixture was washed carefully with a saturated solution of aqueous sodium bicarbonate (10 mL), brine (10 mL) and the dichloromethane was dried (Na_2SO_4) to afford product 2 (93%). MS: 338 (M-1)



3

Diethyl (4-(N-trifuoroacetylamino)-α-bromobenzyl) phosphonate 3:

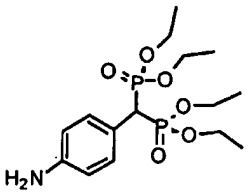
To the above compound 2 (9.75 g, 41.13 mmols) in anhydrous carbon tetrachloride (100 mL) was added NBS (1.6 g , 41.13 mmols) and heated to reflux under intense visible light with stirring under which time a white precipitate formed. The reaction was cooled to rt and then filtered. The filtrate was half concentrated then left in the freezer overnight to crystallize. The crystalline product 3 was seperated by filtration (7.2 g, 60%). MS : 416, 418 (M-1 $Br^{79}Br^{80}$).



4

1-(Bis-diethylphosphonomethylene-4-(N-trifluoroacetylamino)benzene 4:

To compound 3 (7.2 g, 17.22 mmols) in anhydrous THF (50 mL) was added triethylphosphite (0.82 mL, 17mmol) and stirred under reflux for 4 h. Reaction mixture was cooled to rt and concentrated. Residue was taken up in boiling ethyl ether and cooled to rt. Solid was filtered off to afford 6.0 g product (73%). Pale pink solid. MS: 476 (M+H), 475 (M-H).



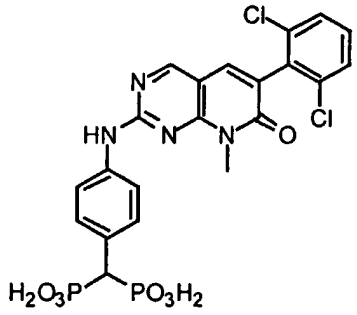
1

1-(Bis-diethylphosphonomethylene)-4-aminobenzene 1:

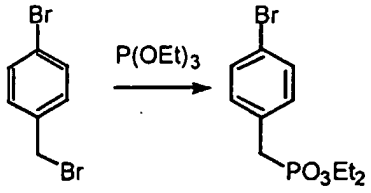
The above N-trifluoroacetate salt 4 (1.2 g, 2.52 mmols) in NaOH solution (0.1 N, 10 mL) was heated to 60 °C for 5 h. The reaction mixture was cooled to rt, and extracted with methylene chloride. Combined organic layers were dried over sodium sulfate and concentrated to afford the product 1 (0.85 g, 97%). MS: 412 (M+23).

Example 4

({4-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-phenyl}-phosphono-methyl)-phosphonic acid

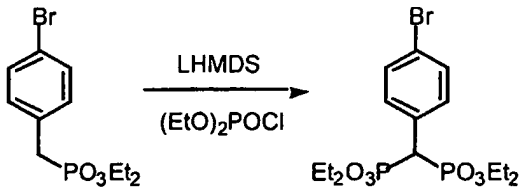


a) (4-Bromo-benzyl)-phosphonic acid diethyl ester



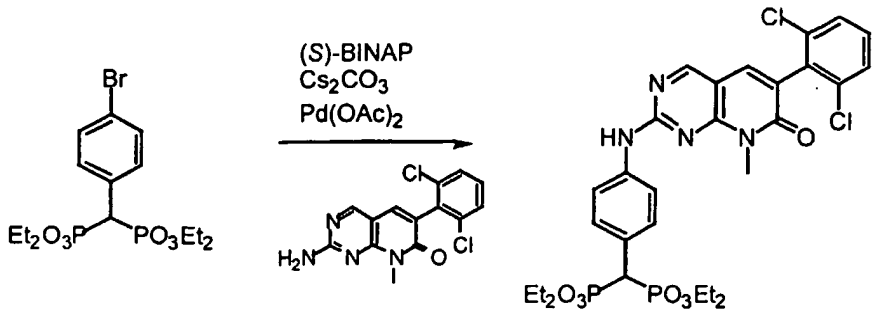
A mixture of triethylphosphite (25 mL, 14.6 mmol) and 4-bromobenzylbromide (2.50 g, 10.0 mmol) was heated to 130 °C and allowed to stir for 5 h. The solution was cooled to rt and chromatographed over silica gel (EtOAc:hexanes, stepwise gradient 1:1 to 100% EtOAc) to give 3.21 g (> 100%) of a yellowish oil. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 307 (M+H).

b) [(4-Bromo-phenyl)-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester



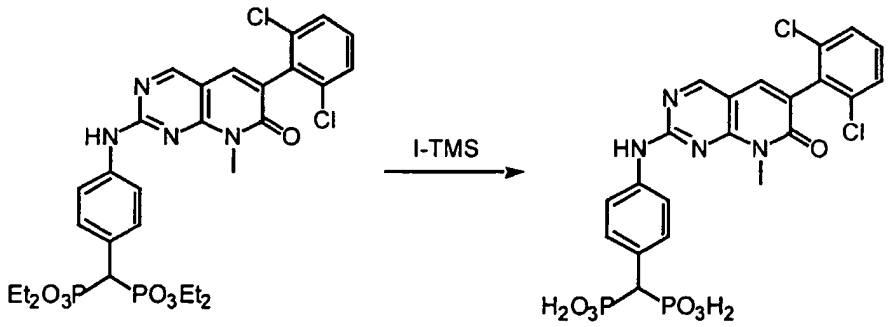
To a cooled (-50 °C) solution of (4-bromo-benzyl)-phosphonic acid diethyl ester (3.21 g, 10.4 mmol) in THF (25 mL) was added a 1M solution of lithium hexamethyldisilylazide in THF (25 mL) over 3 min. Diethylchlorophosphate (2.9 mL, 20 mmol) was added and the mixture was allowed to stir at 50 °C. After 0.5 h, satd NH_4Cl was added and the mixture diluted with EtOAc and H_2O. The aqueous layer was extracted with fresh EtOAc and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed over silica gel ($CHCl_3$:MeOH, stepwise gradient 99:1 to 96:4) to give 1.35 g (29%) of a colorless oil. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 441 (M-H).

c) [{4-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-phenyl}-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester



(4-Bromopyridin-2-yl)-phosphonic acid diethyl ester (64 mg, 0.22 mmol), 2-amino-6-(2,6-dichlorophenyl)pyrido-8-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (60 mg, 0.19 mmol), palladium acetate (3.6 mg, 0.0.016 mmol), [(4-Bromo-phenyl)-(diethoxy-phosphoryl)-methyl]-phosphonic acid diethyl ester (100 mg, 0.23 mmol), (*S*)-BINAP (18 mg, 0.029 mmol) and cesium carbonate (91 mg, 0.28 mmol) were placed in toluene (1 mL), flushed with argon, sealed and heated to 100 °C. After 45 h, the reaction was allowed to cool to rt and diluted with H_2O. The mixture was extracted twice with EtOAc and the combined organic extracts washed with brine and dried over Na_2SO_4. The solution was concentrated and chromatographed over silica gel ($CHCl_3$:MeOH, stepwise gradient 99:1 to 95:5) to give 44 mg (41%) of a yellow solid. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 681 (M-H).

d) ({4-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-phenyl}-phosphono-methyl)-phosphonic acid



To a cooled solution (0 °C) [{4-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-phenyl}-(diethoxy-

phosphoryl)-methyl]-phosphonic acid diethyl ester (44 mg, 0.77 mmol) in MeCN (1.2 mL) was added iodotrimethylsilane (0.3 mL). After 5 h, the reaction was quenched with sodium hydroxide (1 N) and satd sodium thiosulfate. The mixture was filtered and the filtrate chromatographed using reversed-phase HPLC to give 5 mg (11%) of a yellow solid after lyophilization. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 571 (M+H).

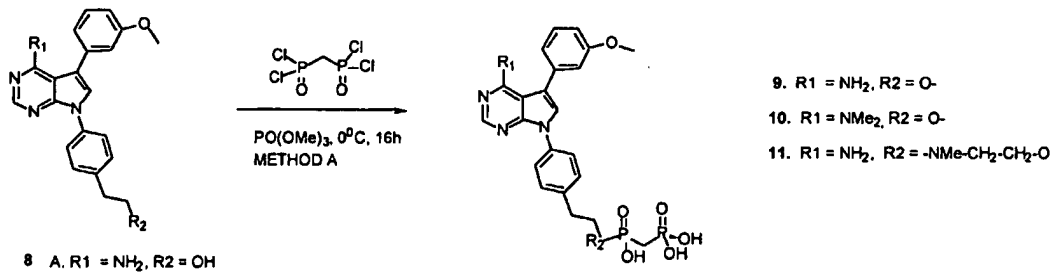
C) Embodiments wherein Tb is ix

Example 5

Synthesis of analogs of 5-(3-methoxyphenyl)-7-[4-(2-hydroxyethylphenyl)-4-aminopyrrolo[2,3-d]-pyrimidine 8 and 5-(3-hydroxyphenyl)-7-[4-(2-hydroxyethylphenyl)-4-aminopyrrolo[2,3-d]pyrimidine 12:

The 8-series and 12-series of compounds were synthesized according to Scheme 3 &Scheme 4. Compounds 9, 10, 11 were synthesized following Scheme 3. Compounds 13 and 14 were sythesized following Scheme 4. Essentially the synthesis consists of phosphorylation of the primary alcohol 12 in Scheme 3 (described in Method A) and demethylation of the methyl ether (described in Method B) followed by phosphorylation in Scheme 4.

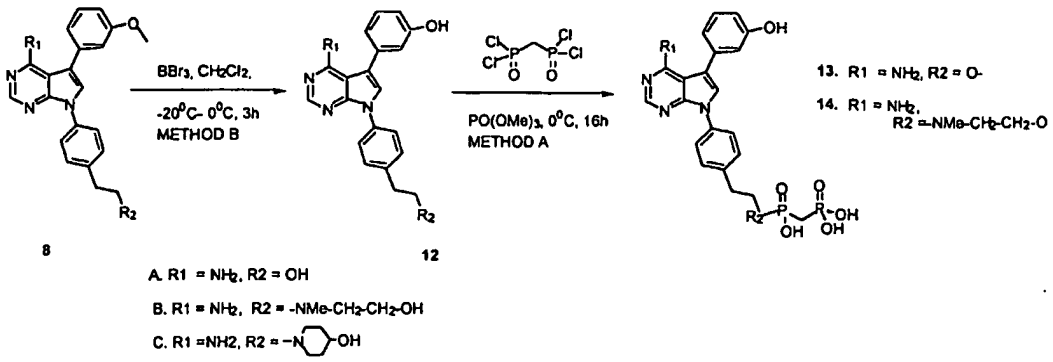
Scheme 3



8 A. R1 = NH_2, R2 = OH
B. R1 = NMe_2, R2 = OH
C. R1 = NH_2, R2 = -NMe-CH_2-CH_2-OH

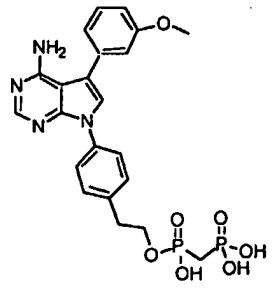
9. R1 = NH_2, R2 = O-
10. R1 = NMe_2, R2 = O-
11. R1 = NH_2, R2 = -NMe-CH_2-CH_2-O

Scheme 4



Method A :

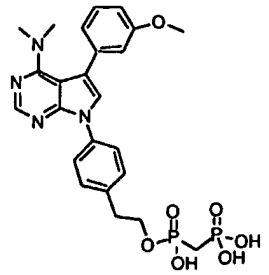
To the alcohol (1 mmol) in trimethylphosphate (1 mL) under anhydrous condition was added the bis-phosphonomethylene dichloride (4 mmol) at 0 °C and stirred at this temp. for 16 h. The reaction mixture was then quenched with ammonium hydroxide and washed with ether. The aqueous layer was purified by preparative HPLC.



9

5-(3-methoxyphenyl)-7-{4-[2-O-(triethylbisphosphonomethylene)ethyl]phenyl)}-4-amino pyrrolo[2,3-d]-pyrimidine 9:

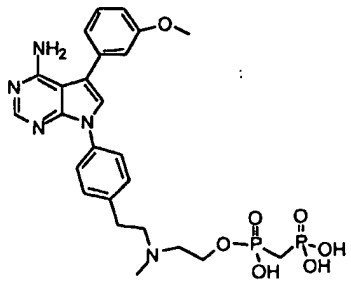
This was prepared from 8A. Purified by HPLC as a white solid. MS: 517 (M-H), 518 (M+H).



10

5-(3-methoxyphenyl)-7-{4-[2-O-(triethylbisphosphonomethylene)ethyl]phenyl}-4-(N,N-dimethylamino pyrrolo[2,3-d]-pyrimidine 10:

This was prepared from 8B. Purified by HPLC as a white solid. MS: 545 (M-H), 547 (M+H).



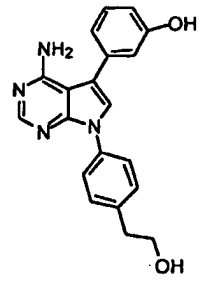
11

5-(3-methoxyphenyl)-7-{4-N-{N'-methyl- [(N'-2'-(O-(triethylbis phosphonomethylene) ethyl} aminoethylphenyl)-4-(amino -pyrrolo[2,3-d]-pyrimidine 11:

This was prepared from 8C. Purified by HPLC as a white solid. MS: 574 (M-H), 576 (M+H).

Method B:

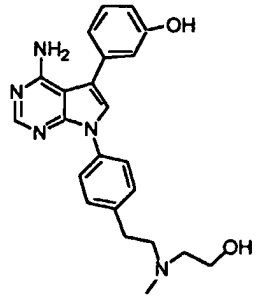
To 1 mmol of methyl ether (8A, 8B & 8C) in methylene chloride (5 mL) was added boron tribromide in methylene chloride (1 M solution, 10 mmol) at 20 °C and after stirring at this temperature for 3 h, reaction was quenched with methanol (5 mL) and concentrated. Compounds were purified by HPLC.



12A

5-(3-Hydroxyphenyl)-7-{4-[2-O- ethylphenyl)-4-aminopyrrolo[2,3-d]-pyrimidine 12A:

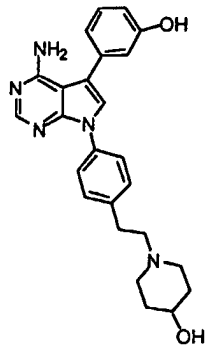
Prepared from 8A following Method B. Off-white solid. MS: 345(M-1), 347 (M+H).



12B

5-(3-Hydroxyphenyl)-7-{4-(2-N-(N'-methyl-N'-2'-hydroxyethyl)-aminoethylphenyl)-4-amino-pyrrolo[2,3-d]-pyrimidine 12B:

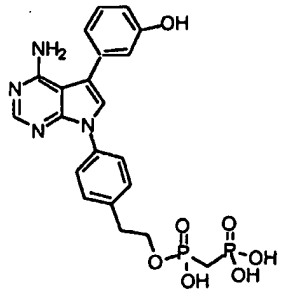
Prepared from 8B using Method B. Off-white solid. MS: 402(M-H), 404 (M+H).



12C

5-(3-Hydroxyphenyl)-7-{4-(2-N-(4'-hydroxypiperidinyl) aminoethylphenyl)-4-amino-pyrrolo[2,3-d]-pyrimidine 12C:

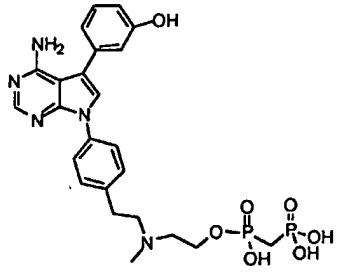
Prepared from 8C using Method B. Off-white solid. MS: 428(M-H), 430 (M+H)



13

5-(3-Hydroxyphenyl)-7-{4-[2-O-(triethylbisphosphonomethylene)ethylphenyl)-4-aminopyrrolo[2,3-d]-pyrimidine 13:

Prepared from 12A using Method A. White solid. MS: 503(M-H), 505(M+H).



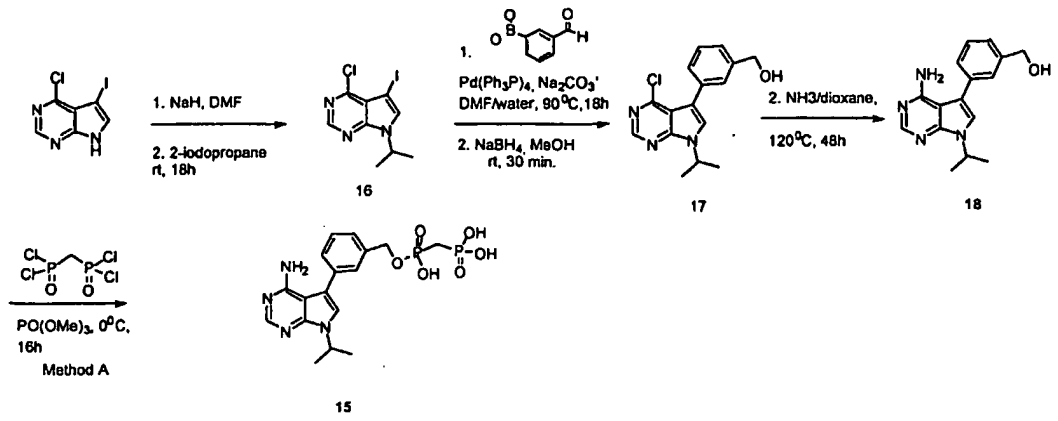
14

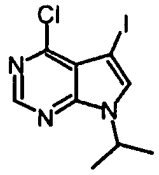
5-(3-Hydroxyphenyl)-7-{4-N-{N'-methyl- [(N'-2'-(O-(triethylbisphosphonomethylene) ethyl) aminoethylphenyl)-4-amino -pyrrolo[2,3-d]-pyrimidine 14:

Prepared from 12B using Method A. White solid. MS : 560 (M-H), 562 (M+H).

Scheme 5 describes the synthesis of compound 15 starting from 5-iodopyrrolo-pyrimidine (J.Med.Chem., 1990).

Scheme 5

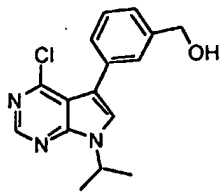




16

4-Chloro-5-iodo-7-isopropyl-pyrrolo[2,3-d]-pyrimidine 16:

To a solution of 4-chloro-5-iodo-7-H-pyrrolo[2,3-d]-pyrimidine (484 mg, 1.729 mmol) in DMF (5 mL) at 0 °C was added sodium hydride (138.4 mg, 60% emulsion, 3.46 mmol). After 30 min at rt., 2-iodopropane (518 μL, 5.19 mmol)was added and the mixture was allowed to stir at rt for 3h. DMF was poured into water and the aqueous later was extracted with ethyl acetate (3 X 30 mL). The organic layer was washed with water (5 mL), dried (sodium sulfate) and concentrated to give a pale yellow solid (520 mg, quantitative). MS: 301(M-H).



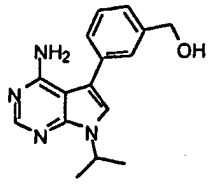
17

4-Chloro-5-(3-hydroxymethyl phenyl)-7-isopropyl-pyrrolo[2,3-d]-pyrimidine 17:

A. To a solution of 4-chloro-5-iodo-7-isopropyl-pyrrolo[2,3-d]-pyrimidine (522 mg, 1.729 mmol)and 3-formylphenylboronic acid (285 mg, 1.902 mmol) in

DMF (13.5mL) was added tetrakis triphenylphosphine palladium(0) (95.58 mg, 0.0865 mmol, 5%) strictly in an argon atmosphere followed by a solution of sodiumbicarbonate (2 M, 1.73 mL) and this mix was heated to 80 °C for 18 h. The reaction was monitored by HPLC. It was diluted with water and extracted with ethyl acetate (50 mL, X 3). Ethyl acetate layer was washed (water), dried (sodium sulfate) and concentrated and the resulting gum was purified by column chromatography on silica gel using hexane/ ethyl acetate to give 306 mg (63%) of pale yellow gum. MS:298 (M-H), 300 (M+H).

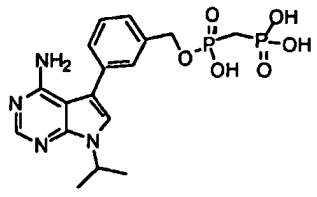
B. To a solution of the above aldehyde (300 mg, 1.008 mmol) in methanol (20 mL) was added sodium borohydride (45 mg, 1.296 mmol) and the reaction was monitored by HPLC. After 1 h methanol was removed *in vacuo*. To the residue was added water (10 mL) and the aqueous layer was extracted in ethyl acetate. Ethyl acetate was dried (sodium sulfate) and concentrated to give a white solid 17 which was used as such in the next step. MS : 300(M-H), 302(M+H).



18

4-Amino-5-(3-hydroxymethyl phenyl)-7-isopropyl-pyrrolo[2,3-d]-pyrimidine 18:

To the above chloro compound (281 mg, 0.931 mmol) in dioxane (10 mL) was added ammonium hydroxide (10 mL) and sealed and heated at 120 °C for 2 days. The solvent was concentrated to give a white solid (200 mg) which was clean enough to take it to the next step. MS : 281(M-H), 282 (M+H).



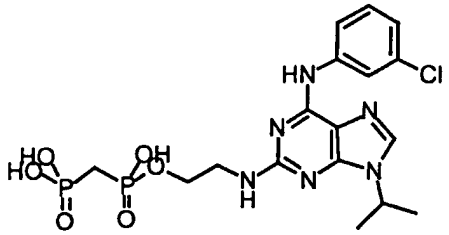
15

4-Amino-5-[(3-O-bisphosphonomethylene methyl)]phenyl-7-isopropyl-pyrrolo[2,3-d]-pyrimidine 15:

Prepared from 18 using Method A as a white solid. MS: 439(M-H), 441(M+H).

Example 6

({2-[6-(3-Chloro-phenylamino)-9-isopropyl-9*H*-purin-2-ylamino]-ethoxy}-hydroxy-phosphorylmethyl)-phosphonic acid



6-Chloro-2-fluoro-9H-purine:

A 0.3 M aqueous solution of $NaNO_2$ (200 mL, 60 mmol) was added dropwise to a cooled (-15 °C), vigorously stirred suspension of 2-amino-6-chloro-9*H*-purine (6.0 g, 35.4 mmol) in 120 mL HBF_4 (48 w% in H_2O, 0.92 mol) over 75 min. The pale yellow reaction was stirred at r. t. for 20 min and then recooled to -15 °C and neutralized to PH = 6.0 with aqueous NaOH (50 w% in H_2O). The water was removed *in vacuo* and the resulting orange solid chromatographed on silica gel (90 : 10 CH_2Cl_2: MeOH, Rf 0.50). The final product was obtained as white solid (3.0 g, 49.1 %).

6-Chloro-2-fluoro-9-isopropyl-9H-purine:

6-Chloro-2-fluoro-9*H*-purine (517.7 mg, 3 mmol), 2-propanol (198.3 mg, 3.3 mmol), PPh_3 (866 mg, 3.3 mmol) was mixed under N_2 in a 50 mL round-bottom flask at 0 °C. DEAD (575 mg, 3.3 mmol) was added via syringe dropwise to the mixture. The temperature was raised to r. t. and the mixture was stirred overnight. Sovent was removed *in vacuo* and the resulting residue was chromatographed on silica gel (CH_2Cl_2/EtOAc, 4:1, Rf 0.62). The product was obtained as a white solid (411 mg, 64 %).

(3-Chlorophenyl)-(2-fluoro-9-isopropyl-9H-purin-6-yl)amine:

6-Chloro-2-fluoro-9-isopropyl-9*H*-purine (214 mg, 1 mmol) was mixed with 3-chloroaniline (127.6 mg, 1 mmol) in 12 mL n-BuOH. DIEA (357.6 mg, 2.8 mmol) was added and the solution was heated at 90 °C overnight. Solvent was removed *in vacuo* and the residue was chromatographed on silica gel (CH_2Cl_2/EtOAc 2:2, Rf 0.44) to get the product as a white solid (148 mg, 48 %).

2-(6-(3-chlorophenylamino-9-isopropyl-9H-purin-2-ylamino)ethanol:

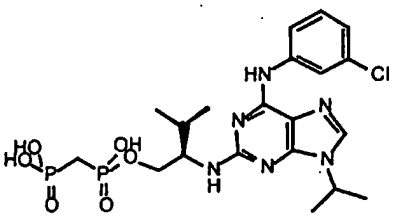
(3-Chlorophenyl)-(2-fluoro-9-isopropyl-9*H*-purin-6-yl)amine (92 mg, 0.3 mmol) and ethanolamine (92 mg, 1.5 mmol) was mixed in 5 mL nBuOH/DMSO (4/1 v/v) and heated at 120 °C overnight. Solvent was removed *in vacuo*. The residue was chromatographed on silica gel (EtOAc, Rf 0.45) to get the product as a greenish solid (24 mg, 90 %).

({2-[6-(3-Chloro-phenylamino)9-isopropyl-9H-purin-2-ylamino]-ethoxy}-hydroxy-phosphorylmethyl)-phosphonic acid:

2-(6-(3-chlorophenylamino-9-isopropyl-9H-purin-2-ylamino)ethanol (180 mg, 0.52 mmol) was dissolved in 3 mL trimethyl phosphate at 0 °C. Methylenebis(phosphonic dichloride) (514 mg, 2.1 mmol) was added in one portion and the reaction was stirred at 0 °C for 16 hrs. The solution was neutralized with 5 N ammonia to PH 6.0. The resulting mixture was purified by RP HPLC. Lyophilization left a white solid (147 mg, 56 %).

Example 7

({2-[6-(3-Chloro-phenylamino)-9-isopropyl-9*H*-purin-2-ylamino]-3-methyl-butoxy}-hydroxy-phosphorylmethyl)-phosphonic acid



(a) 2-(6-(3-chlorophenylamino-9-isopropyl-9H-purin-2-ylamino)-3-methyl-butan-1-ol

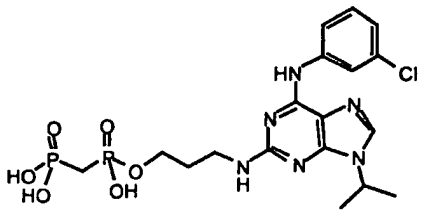
The title compound was synthesized in a manner similar to that described in example 6 (d). ES-MS: m/z 388 (M-H).

(b) ({2-[6-(3-Chloro-phenylamino)-9-isopropyl-9*H*-purin-2-ylamino]-3-methyl-butoxy}-hydroxy-phosphorylmethyl)-phosphonic acid

The title compound was synthesized in a manner similar to that described in example 6 (e). ES-MS: m/z 546 (M-H).

Example 8

({3-[6-(3-Chloro-phenylamino)-9-isopropyl-9*H*-purin-2-ylamino]-propoxy}-hydroxy-phosphorylmethyl)-phosphonic acid



(a) 3-(6-(3-chlorophenylamino-9-isopropyl-9*H*-purin-2-ylamino)-propanol

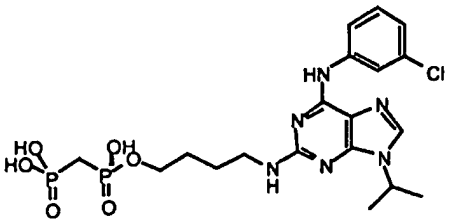
The title compound was synthesized in a manner similar to that described in example 6 (d). ES-MS: m/z 360 (M-H).

(b) ({2-[6-(3-Chloro-phenylamino)-9-isopropyl-9*H*-purin-2-ylamino]-propoxy}-hydroxy-phosphorylmethyl)-phosphonic acid

The title compound was synthesized in a manner similar to that described in example 6 (e). ES-MS: m/z 518 (M-H).

Example 9

({4-[6-(3-Chloro-phenylamino)-9-isopropyl-9*H*-purin-2-ylamino]-butoxy}-hydroxy-phosphorylmethyl)-phosphonic acid



(a) 4-(6-(3-chlorophenylamino-9-isopropyl-9*H*-purin-2-ylamino)-butanol

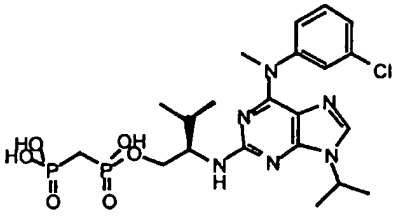
The title compound was synthesized in a manner similar to that described in example 6 (d). ES-MS: m/z 374 (M-H).

(b) ({2-[6-(3-Chloro-phenylamino)-9-isopropyl-9*H*-purin-2-ylamino]-butoxy}-hydroxy-phosphorylmethyl)-phosphonic acid

The title compound was synthesized in a manner similar to that described in example 6 (e). ES-MS: m/z 532 (M-H).

Example 10

({2-[6-(3-Chloro-phenylamino)-9-isopropyl-9*H*-purin-2-ylamino]-3-methyl-butoxy}-hydroxy-phosphorylmethyl)-phosphonic acid



(a) (3-Chloro-phenyl)-(2-fluoro-9-isopropyl-9*H*-purin-6-yl)-methyl-amine

The title compound was synthesized in a manner similar to that described in example 6 (c). ES-MS: m/z 319 (M-H).

(b) 2-{6-[(3-chloro-phenyl)-methyl-amino]-9-isopropyl-9*H*-purin-2-ylamino}-3-methyl-butan-1-ol

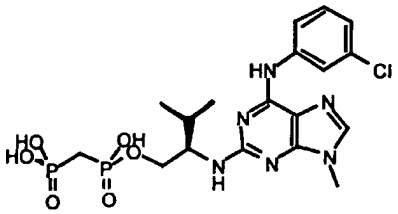
The title compound was synthesized in a manner similar to that described in example 6 (d). ES-MS: m/z 402 (M-H).

(c) [(2-{6-[(3-Chloro-phenyl)-methyl-amino]-9-isopropyl-9*H*-purin-2-ylamino}-3-methyl-butoxy)-hydroxy-phosphorylmethyl]-phosphonic acid

The title compound was synthesized in a manner similar to that described in example 6 (e). ES-MS: m/z 560 (M-H).

Example 11

({2-[6-(3-Chloro-phenylamino)-9-methyl-9*H*-purin-2-ylamino]-3-methyl-butoxy}-hydroxy-phosphorylmethyl)-phosphonic acid



(a) 6-Chloro-2-fluoro-9-methyll-9*H*-purine

The title compound was synthesized in a manner similar to that described in example 6 (b). ES-MS: m/z 186 (M-H).

(b) (3-Chloro-phenyl)-(2-fluoro-9-methyl-9*H*-purin-6-yl) -amine

The title compound was synthesized in a manner similar to that described in example 6 (c). ES-MS: m/z 276 (M-H).

(c) 2-[6-(3-chloro-phenylamino)-9-isopropyl-9*H*-purin-2-ylamino]-3-methyl-butan-1-ol

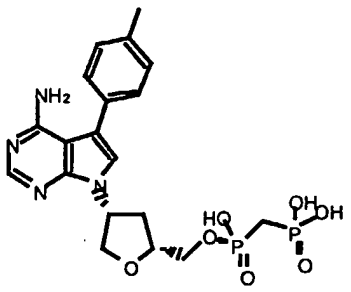
The title compound was synthesized in a manner similar to that described in example 6 (d). ES-MS: m/z 360 (M-H).

(d) [{2-[6-(3-Chloro-phenylamino)-9-methyl-9*H*-purin-2-ylamino]-3-methyl-butoxy}-hydroxy-phosphorylmethyl)-phosphonic acid

The title compound was synthesized in a manner similar to that described in example 6 (e). ES-MS: m/z 518 (M-H).

Example 12

{[4-(4-Amino-5-*p*-tolyl-pyrrolo[2,3-*d*]pyrimidin-7-yl)-tetrahydrofuran-2-ylmethoxyl]-hydroxy-phosphorylmethyl} phosphonic acid



(a) 7-Benzenesulfonyl-4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine

To 4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.26 g, 4.5 mmol) in 45 mL dry THF was added NaH (217 mg, 9.0 mmol). The mixture was stirred at r. t. for 1 hr. $PhSO_2Cl$ (875 mg, 5.0 mmol) was added via syringe dropwise. Stirring was continued for another 2 hrs. Solvent was removed *in vacuo*. The residue was diluted with ice-H_2O and then neutralized with saturated NH_4Cl 13.5 mL. The mixture was extracted with CH_2Cl_2 (2 X 60 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Solvent was removed *in vacuo* and residue was chromatographed on silica gel (CH_2Cl_2, Rf 0.44). The product was obtained as a white solid (1.12 g, 59 %).

(b) 7-Benzenesulfonyl-4-chloro-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine

7-Benzenesulfonyl-4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.12 g, 2.67 mmol), 4-methylbenzeneboronic acid (373 mg, 2.74 mmol) and $NaHCO_3$ (693 mg, 8.25 mmol) was mixed with EtOH (6 mL), toluene (43 mL) and H2O (12 mL). The mixture was bubbled with Ar for 1 hour before $Pd(PPh_3)_2Cl_2$ (189 mg, 0.27 mmol) was added. The reaction mixture was heated at 95 °C overnight. After cooling to r. t., the reaction mixture was filtered through a pad of Celite. The filtrate was partitioned between EtOAc and water, organic layer was separated, dried and concentrated.

Residue was chromatographed on silica gel (3/1 hexane/EtOAc, Rf 0.34) to get product as a white solid (0.74 g, 74 %).

(c) 4-Chloro-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine

7-Benzenesulfonyl-4-chloro-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (740 mg, 1.93 mmol) in 50 mL THF was added TBAF 1.93 mL (1.0 M solution in THF). The reaction mixture was heated under reflux for 1.5 hrs. The solvent was removed *in vacuo*. The residue was partitioned between EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 X). Combined organic layer was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (2/1 CH_2Cl_2/EtOAc, Rf 0.42) to give product as a white solid (343 mg, 73%).

(d) 4-Amino-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine

4-Chloro-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (220 mg, 0.9 mmol) was dissolved in 5 mL dioxane in a pressure tube and then concentrated ammonia 5 mL was added. The mixture was heated at 120 °C for 4 days. Solvent was removed and the resulting residue was partitioned between EtOAc/H_2O. Organic layer was separated and the aqueous layer was extracted with EtOAc (3 X). Combined organic layer was dried (Na_2SO_4), concentrated to provide crude product as a white solid (202 mg, ~100%).

(e) Toluene-4-sulfonic acid 5-dimethoxymethyl-tetrahydro-furan-3-yl ester

The title compound was synthesized according to the procedure described in *Tetrahedron Lett.* **1989**, *30*, 6259-6262.

(f) 7-(5-Dimethoxymethyl-tetrahydro-furan-3-yl)-5-p-tolyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-ylamine

To 4-amino-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (250 mg, 1.2 mmol), 18-Crown-6 (316 mg, 1.2 mmol) in 32 mL dry DMF was added K_2CO_3 (326 mg, 2.4 mmol). The mixture was stirred at r.t. for 30 min. Then toluene-4-sulfonic acid 5-dimethoxymethyl-tetrahydro-furan-3-yl ester (100 mg, 1.2 mmol) in 15 mL DMF was

added and the reaction was heated at 80 °C overnight. After cooling to r.t., the mixture was partitioned between EtOAc and water, organic layer was separated and the aqueous layer was extracted with EtOAc (3 X). Combined organic layer was dried (Na_2SO_4), concentrated and the residue was chromatographed on silica gel (10 % MeOH in EtOAc, Rf 0.38). The product is obtained as a liquid (357 mg, 80 %).

(g) [4-(4-Amino-5-*p*-tolyl-pyrrolo[2,3-*d*]pyrimidin-7-yl]-tetrahydrofuran-2-yl]-methanol

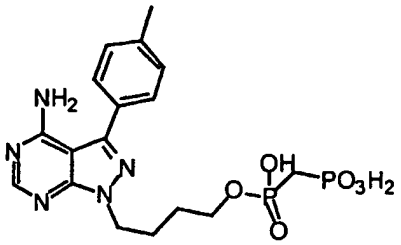
7-(5-Dimethoxymethyl-tetrahydro-furan-3-yl)-5-p-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamine (357 mg, 1 mmol) was dissolved in 10 mL dioxane and 1 % TFA/H_2O 10 mL was added and the mixture was heated at 80 °C overnight. The solution was added 1 N NaOH until PH = 6.0. $NaBH_4$ (38 mg, 1 mmol) was added and the solution was stirred at r. t. for 10 min. Solvent was removed *in vacuo* and the resulting residue was partitioned between EtOAc and H_2O. Organic layer was separated and the aqueous layer was extracted with EtOAc (3 X). Combined organic layer was dried (Na_2SO_4), concentrated and the residue was chromatographed on silica gel (10 % MeOH in EtOAc, Rf 0.38). The product was obtained as a white solid (201 mg, 62 %).

(h) {[4-(4-Amino-5-*p*-tolyl-pyrrolo[2,3-*d*]pyrimidin-7-yl)-tetrahydrofuran-2-ylmethoxyl]-hydroxy-phosphorylmethyl} phosphonic acid

[4-(4-Amino-5-*p*-tolyl-pyrrolo[2,3-*d*]pyrimidin-7-yl]-tetrahydrofuran-2-yl]-methanol was dissolved in 4 mL trimethyl phosphate and was cooled to -5-0 °C. Methylenebis (phosphonic dichloride) (212 mg, 0.8 mmol) was added in one portion and the resulting mixture was stirred at that temperature for 2 hrs. The reaction mixture was transferred via syringe to 20 mL cold 10 % $NaHCO_3$. The mixture was neutralized with 1 N HCl, and then purified by RP HPLC. The final product was obtained as a white solid (31 mg, 32%). ES-MS: m/z 481 (M-H).

Example 13

{[4-(4-Amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-butoxy]-hydroxy-phosphorylmethyl}-phosphonic acid



(a) Acetic acid 4-(4-amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-butyl ester

The title compound was made according to the procedure detailed in J. Med. Chem. **1990**, *33*, 1980-1983.

(b) 4-(4-Amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-butan-1-ol

Acetic acid 4-(4-amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-butyl ester (0.85 g, 2.5 mmol), and $LiOH \cdot H_2O$ (0.25 g, 5.96 mmol) were dissolved in THF (3 mL)/H_2O (10 mL) and heated to 70 °C for 2 h. After cooling, the mixture was dumped into water and extracted with EtOAc. The combined extracts were washed with water, dried over magnesium sulfate, and concentrated to a yellow solid which was used without purification in the next reaction (0.20 g, 27%).

(c) Toluene-4-sulfonic acid 4-(4-amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-butyl ester

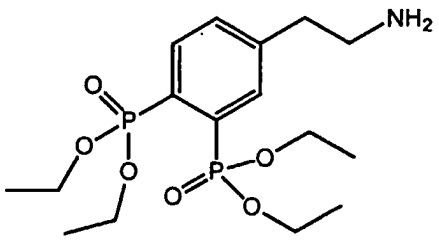
A mixture of 4-(4-amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-butan-1-ol (0.19 g, 0.66 mmol), TsCl (0.28 g, 1.50 mmol), DMAP (0.19 g, 1.56 mmol) and CH_2Cl_2 (10 mL) were stirred for 24 h at rt. The mixture was dumped into water and extracted with CH_2Cl_2. The combined extracts were washed with water, dried over magnesium sulfate, and concentrated to a yellow solid which was purified over silica gel (1% MeOH/CH_2Cl_2) to yield a white foam (0.25 g, 85%). MS $[M + H]^+$ 452.

(d) {[4-(4-Amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-butoxy]-hydroxy-phosphorylmethyl}-phosphonic acid

The title compound was made following the procedure detailed in JOC **1987**, *52*, 1794. MS [M - H]$^-$ 454.

D) Embodiments wherein Tb is x

Bis-3,4-(diethylphophonyl)-β-phenylethyl amine 5



5

N-t-butoxycarbonyl-3-hydroxytyramine

To a solution of 3-hydroxytyramine hydrochloride (5.0 g, 26.36 mmol) in dixane/water (50/30 mL) at 0 °C was added sodium bicarbonate (6.64g, 79.08 mmol) and stirred for 10 min. To this was added Boc anhydride (7.48 g, 34.275 mmol) and stirred at rt for 18 h. After removing dioxane in vacuo, the slurry was taken up in water (~60 mL) and extracted in ethyl acetate (25 mL X 3). The organics were washed with 1N HCl (10 mL X 2) followed by brine (10mL); dried (sodium sulfate) and concentrated which when cooled in the refregerator crystallized the next day (3.87 g, 57%). MS: 252 (M-H).

N-t-butoxycarbonyl-bis-3,4-O-triflyl-β-phenylethyl amine

To a solution of N-Boc-3-hydroxytyramine (3.87 g, 15.28 mmol) in anhydrous dichloromethane (70 mL) was added triethyl amine (61.12 mmol) followed by N-phenyl triflamide (16.37 g, 45.84 mmol) and stirred at rt for 24 h. Reaction mixture was diluted with dichloromethane (100 mL) and washed successively with 1N HCl (3X 10 mL) and brine (10 mL) and dried (sodium sulfate). After concentration of dichloromethane extract the brown oil was chromatographed on silicagel using hexane /ethyl acetate (10-100%) to give product as a viscous oil (6.32 g, 80%). MS: 516 (M-H).

N-t-butoxycarbonyl-bis-3,4-(diethylphophonyl)-β-phenylethyl amine

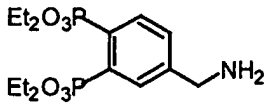
To the N-t-butoxycarbonyl-bis-3,4-O-triflyl-β-phenylethyl amine (6.32 g, 12.21 mmol) in acetonitrile in an atmosphere of argon was carefully added diethyl phosphite (3.46 mL, 26.87 mmol), N-methylmorpholine (3.09 mL, 30.54 mmol), tetrakistriphenylphosphine palladium(0) (1.41 g, 1.221 mmol) and after flushing the solution with argon for 10 min. it was stoppered and heated to 90 °C for 2 days. Acetonitrile was concentrated, and the residue was diluted with ethyl acetate. The organic layer was washed with citric acid (10%, 10 mL X2), brine (10 mL) and dried (sodium sulfate). The yellow gum after concentration of ethyl acetate was purified by flash column chromatography on silica gel using ethyl acetate in hexane (33%-100%) followed by ethyl acetate/methanol (9/1) to give a pale yellow gum (992 mg, 16.5%). MS: 492(M-H).

Bis-3,4-(diethylphophonyl)-β-phenylethyl amine

To the N-t-butoxycarbonyl-bis-3,4-(diethylphophonyl)-β-phenylethyl amine (0.992 g, 2.01 mmol) in dichloromethane (10 mL) was added TFA (25% in dichloromethane, 2.5 mL). After 1.5 h the solvents were removed in vacuo and the residue was diluted with saturated sodium bicarbonate and dichloromethane (5 mL and 50 mL). The aqueous layer was re extracted with dichloromethane (25 mL X 2). Combined organics were concentrated to give a pale brown gum (0.758 g, 96%) which was pure enough for the next step. MS:392 (M-H), 416 (M+23).

Example 14

[4-Aminomethyl-2-(diethoxy-phosphoryl)-phenyl]-phosphonic acid diethyl ester



(b) (3,4-Dihydroxy-benzyl)-carbamic acid *tert*-butyl ester

4-Aminomethyl-benzene-1,2-diol hydrobromide (5.6 g, 25.2 mmol) was dissolved in CH_3CN/H_2O 1:1 (100 mL). $NaHCO_3$ (4.3 g, 50.4 mmol) was added followed by Boc_2O (5.5 g, 25.2 mmol). The mixture was stirred for 18 h,

concentrated, and extracted with EtOAc. The combined extracts were washed with water, dried over magnesium sulfate, and concentrated to a tan solid which was used without purification in the next reaction.

(c) Trifluoro-methanesulfonic acid 5-*(tert*-butoxycarbonylamino-methyl)-2-trifluoromethanesulfonyloxy-phenyl ester

(3,4-Dihydroxy-benzyl)-carbamic acid *tert*-butyl ester (5.5 g, 23.0 mmol), N-phenyltrifluoromethanesulfonimide (26.9 g, 75 mmol), and Et_3N (14.9 mL, 107 mmol) were dissolved in CH_2Cl_2 (80 mL) and stirred for 24 h. The mixture was dumped into water and the layers seperated. The aqueous layer was extracted with methylene chloride. The combined extracts were washed with water, dried over magnesium sulfate, concentrated, and purified by silica gel chromatography (hexane/EtOAc 3:1) to yield the product as a brown oil (9.0 g, 78%).

(d) [4-(*tert*-Butoxycarbonylamino-methyl)-2-(diethoxy-phosphoryl)-phenyl]-phosphonic acid diethyl ester

Trifluoro-methanesulfonic acid 5-*(tert*-butoxycarbonylamino-methyl)-2-trifluoromethanesulfonyloxy-phenyl ester (5 g, 10.o mmol), diethyl phosphite (2.8 mL, 20.3 mmol), N-methylmorpholine (2.7 mL, 25.1 mmol) and tetrakis(triphenylphosphine)-palladium(0) (1.2 g) were dissolved in anhydrous acetonitrile (100 mL) and heated in a sealed tube at 90 °C for 48 h. After cooling, the mixture was diluted with EtOAc (200 mL) and washed with water, 1 N HCl and brine. The organic layer was dried over magnesium sulfate, concentrated, and purified by silica gel chromatography (5% MeOH/$CHCl_3$) to yield the product as a colorless oil (2.0 g, 42%). ^{1}H NMR (300 Mhz, $CDCl_3$) δ 1.35 (m, 12 H), 3.79 (bs, 2 H), 3.96 (m, 8H), 7.45 (m, 1H), 7.91 (m, 2H).

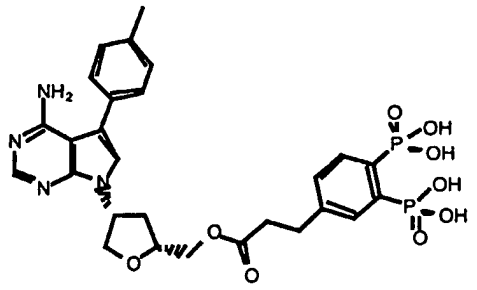
(e) [4-Aminomethyl-2-(diethoxy-phosphoryl)-phenyl]-phosphonic acid diethyl ester

[4-(*tert*-Butoxycarbonylamino-methyl)-2-(diethoxy-phosphoryl)-phenyl]-phosphonic acid diethyl ester (2.0 g, 4.2 mmol) was dissolved in TFA/CH_2Cl_2 (25%, 20 mL) and stirred for 3 h. The mixture was evaporated under a stream of N_2, dissolved in EtOAc and washed with sat'd $NaHCO_3$. The organic layer was dried over

magnesium sulfate, and concentrated to a brown oil (0.9 g, 2.3 mmol) which was used without purification in the next reaction.

Example 15

3-(3,4-Bis-phosphono-phenyl)-propionic acid 4-(4-amino-5-p-tolyl-pyrrolo[2,3-d]pyrimidin-7-yl)-tetrahydro-furan-2-ylmethyl ester



(a) 3-[3,4-Bis-(diethoxy-phosphoryl)-phenyl]-propionic acid 4-(4-amino-5-*p*-tolyl-pyrrolo[2,3-*d*]pyrimidin-7-yl)-tetrahydro-furan-2-ylmethyl ester

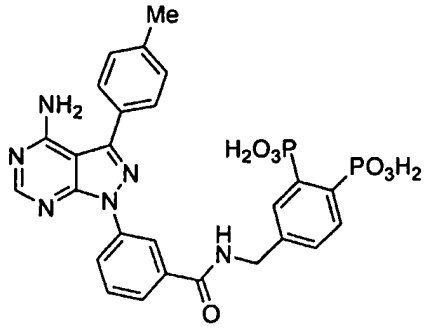
[4-(4-Amino-5-*p*-tolyl-pyrrolo[2,3-*d*]pyrimidin-7-yl]-tetrahydrofuran-2-yl]-methanol (32.4 mg, 0.1 mmol), 3-[3,4-bis-(diethoxy-phosphoryl)-phenyl]-propionic acid (47 mg, 0.11 mmol), DCC (22.7 mg, 0.11 mmol) and DMAP (5 mg, 0.041 mmol) was mixed in 2 mL dry DMF under N_2. The reaction mixture was stirred at r.t. overnight. The product was purified by RP HPLC to get a liquid (17 mg, 25 %).

(b) 3-(3,4-Bis-phosphono-phenyl)-propionic acid 4-(4-amino-5-p-tolyl-pyrrolo[2,3-d]pyrimidin-7-yl)-tetrahydro-furan-2-ylmethyl ester

3-[3,4-Bis-(diethoxy-phosphoryl)-phenyl]-propionic acid 4-(4-amino-5-*p*-tolyl-pyrrolo[2,3-*d*]pyrimidin-7-yl)-tetrahydro-furan-2-ylmethyl ester (18 mg, 0.025 mmol) was dissolved in 2 mL dry acetonitrile under N_2. The solution was cooled to -12 °C. TMSI (100 mg, 0.5 mmol) was added via syringe and the reaction was stirred at that temperature for 16 hrs. To the solution was added 10 % $NaHCO_3$ until pH = 7.0. Then a few drops of sat. $Na_2S_2O_3$ was added just enough to make the yellow color disappear. The resulting mixture was purified by RP HPLC. The final product is a white powder (6.5 mg, 42 %). ES-MS: m/z 616 (M-H).

Example 16

(4-{[3-(4-Amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-benzoylamino]-methyl}-2-phosphono-phenyl)-phosphonic acid



(a) 3-(4-Amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-benzoic acid

The title compound was made as for example 19(b).

(b) [4-{[3-(4-Amino-3-*p*-tolyl-pyrazolo[3,4-*d*]pyrimidin-1-yl)-benzoylamino]-methyl}-2-(diethoxy-phosphoryl)-phenyl]-phosphonic acid diethyl ester

3-(4-Amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-benzoic acid (0.015 g, 0.043 mmol), [4-aminomethyl-2-(diethoxy-phosphoryl)-phenyl]-phosphonic acid diethyl ester (0.021 g, 0.054 mmol), HOBt (0.007 g, 0.052 mmol), and EDC•HCl (0.01 g, 0.052 mmol) were dissolved in DMF (1 mL) and stirred at rt for 1h. Purification by RP HPLC (CH_3CN/H_2O) and lyophylization yielded a white powder (0.023 g, 75%). MS $[M + H]^+$ 708.

(c) (4-{[3-(4-Amino-3-*p*-tolyl-3a,7a-dihydro-pyrazolo[3,4-*d*]pyrimidin-1-yl)-benzoylamino]-methyl}-2-phosphono-phenyl)-phosphonic acid

[4-{[3-(4-Amino-3-*p*-tolyl-pyrazolo[3,4-*d*]pyrimidin-1-yl)-benzoylamino]-methyl}-2-(diethoxy-phosphoryl)-phenyl]-phosphonic acid diethyl ester (0.023 g, 0.033 mmol) dissolved in CH_3CN (1 mL) was treated with TMSI (0.093 mL, 0.65 mmol). The mixture was stirred for 4 h, made basic with 1N NaOH, and decolorized with solid $NaSHO_3$. The resulting solution was diluted with DMF (5 mL) and

purified by RP HPLC (CH_3CN/H_2O). Lyophylization yielded a white powder (0.011 g, 75%). MS $[M - H]^-$ 593.

E) Embodiments wherein Tb is xii

General Scheme for Embodiments wherein Tb is a subsituted aryl:

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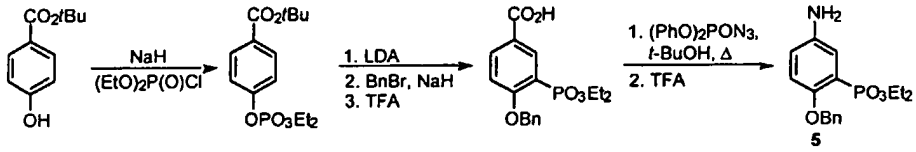
Example 17



Synthesis of aniline 5

(a) To a suspension of NaH (220 mg of a 60% dispersion in mineral oil (5.5 mmol), washed three times with hexanes) in THF (15 mL) at rt under N_2 was added *t*-butyl 4-hydroxybenzoate (971 mg, 5.0 mmol) in one portion. After H_2 evolution ceased (~10 min.), diethyl chlorophosphate (0.79 mL, 5.5 mmol) was added. The reaction mixture was stirred at rt overnight and then poured into 1.0 *N* aq NaOH (20 mL) and extracted with EtOAc. The organic extract was washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated. The crude oil was purified by flash chromatography on silica gel. Elution with 2:1 hexanes-EtOAc followed by 1:1 hexanes-EtOAc afforded 1.48 g (90%) of the phosphate as a colorless oil.

(b) To a solution of *i*-Pr_2NEt (1.2 mL, 8.48 mmol) in THF (22 mL) at 0 °C under N_2 was slowly added 1.6 *M n*-BuLi in hexanes (5.3 mL, 8.48 mmol). After 10 min., the LDA solution was cooled to -78 °C, and a solution of the phosphate (1.40 g, 4.24 mmol) in THF (5 mL) was slowly added via cannula. A 2 mL rinse of the flask was also added. The reaction mixture was stirred at -78 °C for 2 h and at 0 °C for 1 h. The reaction mixture was then diluted with half saturated aq NH_4Cl (20 mL). The mixture was further acidified by the addition of a small amount of 6 *N* aq HCl, and then extracted with EtOAc. The extract was washed with H_2O (10 mL) and brine (10

mL). The aqueous washes were reextracted once with EtOAc, and the combined extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 5:1 hexanes-EtOAc followed by 3:1 hexanes-EtOAc afforded 1.32 g (94%) of the desired phosphonate as a light yellow oil.

(c) To a solution of the phenol (1.30 g, 3.94 mmol) in CH_3CN (10 mL) at rt under N_2 was added K_2CO_3 (600 mg, 4.33 mmol) followed by benzyl bromide (0.51 mL, 4.33 mmol). The reaction mixture was stirred at 50 °C. After cooling, the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The extract was dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel to afford 1.86 g (quant) of the desired benzyl ether.

(d) To a solution of the *t*-butyl ester (from above) in CH_2Cl_2 (12 mL) at 0 °C under N_2 was slowly added TFA (4 mL). The resulting solution was stirred at 0 °C for 1 h and at rt for 3 h. The reaction mixture was then concentrated under a stream of N_2 followed by high vacuum to afford the desired acid as an off-white solid.

(e) To a solution of the acid (364 mg, 1.00 mmol) in 1:1 toluene-*t*-BuOH (4 mL) at rt under N_2 was added *i*-Pr_2NEt (0.44 mL, 2.5 mmol) followed by $(PhO)_2P(O)N_3$ (0.54 mL, 2.5 mmol). The resulting solution was then stirred at reflux for 5 h. The yellow solution was allowed to cool to rt and was then partitioned between EtOAc and H_2O (20 mL). The layers were separated, and the organic extract was then washed with H_2O (20 mL) and brine (20 mL). The EtOAc extract was then dried over Na_2SO_4 and concentrated. The crude was purified by flash chromatography on silica gel. Elution with 1:1 EtOAc-hexanes followed by 2:1 EtOAc-hexanes afforded 146 mg (34%) of the desired carbamate.

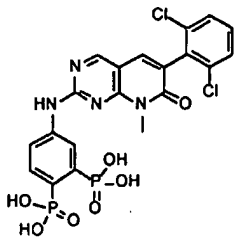
(f) To a solution of the carbamate (879 mg, 2.02 mmol) in CH_2Cl_2 (8 mL) at rt under N_2 was added TFA (2 mL). The solution was stirred at rt for 3 h and then concentrated under a stream of N_2. The residue was purified by flash chromatography

on silica gel. Elution with 3:1 EtOAc-hexanes followed by 15:1 $CHCl_3$-MeOH afforded 612 mg of aniline **5**.

Condensation of aniline 5 with sulfone 1 and subsequent deprotection to 9

(a) A mixture of aniline **5** (605 mg, 1.80 mmol) and sulfone **1** (347 mg, 0.902 mmol) in 2-methoxyethyl ether (5 mL) was stirred at 150 °C for 2 h. The dark solution was allowed to slowly cool to rt overnight. The precipitate that had formed was then filtered, washed with Et_2O and dried under high vacuum to afford 310 mg (54%) of the desired coupling product.

(b) A solution of the coupling product (from above, 39 mg, 0.610 mmol) in AcOH (~3-4 mL) containing a catalytic amount of 10% Pd/C was stirred under an atmosphere of N_2 (double stuffed balloon) for 3 h. The reaction mixture was then filtered through a pad of Celite, and the filtrate concentrated. The residue was purified by flash chromatography on silica gel. Elution with 1:1 EtOAc-hexanes afforded 24 mg (72%) of phenol **9**.

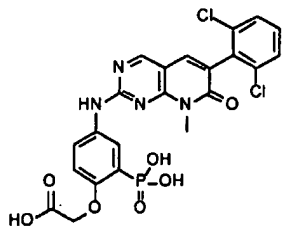


***x*-A**

(a) To a solution of phenol **9** (85 mg, 0.155 mmol) and *i*-Pr_2NEt (0.03 mL, 0.186 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 was added $PhNTf_2$ (72 mg, 0.201 mmol). The reaction mixture was stirred at rt for 5 days. Additional *i*-Pr_2NEt and $PhNTf_2$ was added, and the reaction mixture stirred for an additional day. The reaction mixture was then diluted with EtOAc and washed with 1.0 *M* aq HCl (10 mL), H_2O (10 mL), and brine (10 mL). The EtOAc extract was dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 1:1 EtOAc-hexanes, 3:2 EtOAc-hexanes and finally 2:1 EtOAc-hexanes afforded 90 mg (86%) of the triflate.

(b) To a solution of the triflate (43.8 mg, 0.0644 mmol) in CH_3CN (1.0 mL) at rt under N_2 was added NMM (0.01 mL, 0.0911 mmol), $(EtO)_2POH$ (0.011 mL, 0.0841 mmol) and a catalytic amount of $Pd(PPh_3)_4$. The mixture was then stirred at 70 °C overnight. The reaction mixture was then partitioned between EtOAc and 1.0 *M* aq HCl. The layers were separated and the organic layer was washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silica gel to afford an inseparable mixture of the desired bisphosphonate and **9**, which was used in the next reaction without further purification.

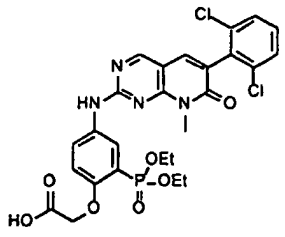
(c) The mixture of products from above was converted to ***x*-A** in the same fashion as previously described (***i*-A, (b)**).



***x*-B**

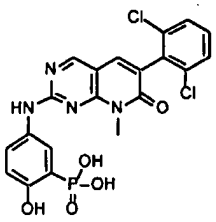
(a) To a solution of phenol **9** (17.9 mg, 0.0326 mmol) in CH_3CN containing Cs_2CO_3 (16 mg, 0.0489 mmol) at rt under N_2 was added *t*-butyl bromoacetate (0.006 mL, 0.0424 mmol). The yellow color of the reaction mixture slowly disappeared over time, and after 3 h, the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The EtOAc layer was dried over Na_2SO_4 and concentrated. The crude residue was used without further purification.

(b) The crude residue from above was converted to ***x*-B** in the same fashion as previously described (***i*-A, (b)**).



x-C

The crude residue from above (*x*-B, (a)) was converted to *x*-C in the same fashion as previously described (*i*-A, (b)) except that the reaction mixture was only allowed to warm to 0 °C before being quenched.



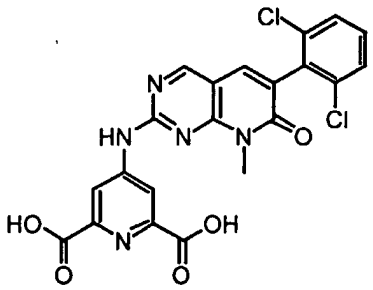
x-D

Phenol **9** was converted to *x*-**D** in the same fashion as previously described (*i*-A, (b)).

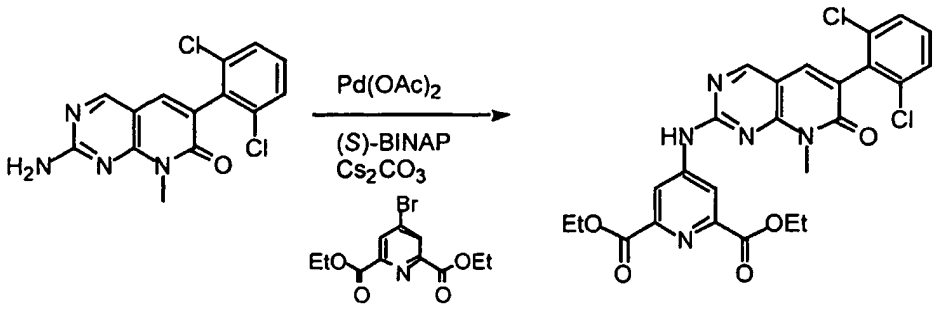
F) Embodiments wherein Tb is xiii

Example 18

4-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridine-2,6-dicarboxylic acid

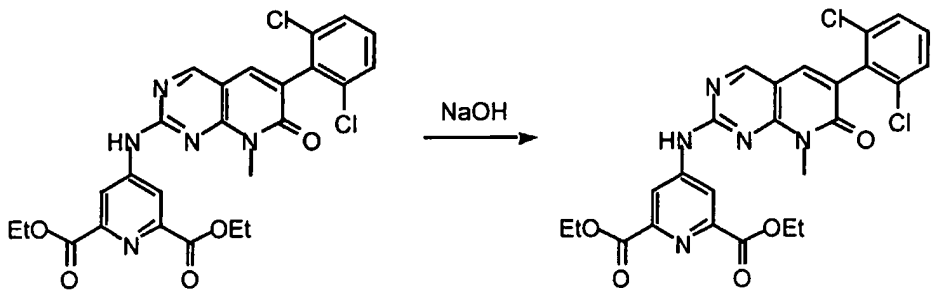


a) 4-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridine-2,6-dicarboxylic acid diethyl ester



4-Bromo-pyridine-2,6-dicarboxylic acid diethyl ester (39 mg, 0.13 mmol), 2-amino-6-(2,6-dichlorophenyl)pyrido-8-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (50 mg, 0.16 mmol), 4-bromopyridine-2,6-dicarboxylic acid diethyl ester (39 mg, 0.13 mmol), palladium acetate (1.5 mg, 0.0067 mmol), (*S*)-BINAP (6.0 mg, 0.0096 mmol) and cesium carbonate (60 mg, 0.18 mmol) were placed in toluene (0.5 mL). The flask was purged with argon, sealed and heated to 100 °C. After 20 h, the reaction was allowed to cool to rt and diluted with EtOAc and H_2O. The aqueous layer was extracted with fresh EtOAc, the organic fractions combined, washed with brine and dried over Na_2SO_4. The solution was concentrated and chromatographed over silica gel using $CHCl_3$:MeOH (99:1) to provide 49 mg (69%) of a yellow solid. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 540 (M-H).

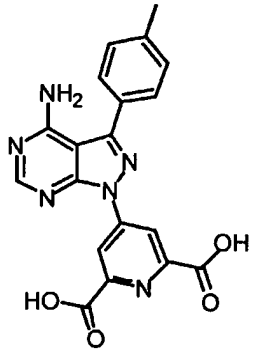
b) 4-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridine-2,6-dicarboxylic acid



To a solution of 4-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridine-2,6-dicarboxylic acid diethyl ester (49 mg, 0.090 mmol) in MeOH (0.5 mL) was added 1N sodium hydroxide (0.36 mL) resulting in a suspension. A solution was obtained after addition of water (0.5 mL) and heating to 80 °C. After 3 h, the reaction was allowed to cool to rt, diluted with MeCN/H_2O/DMF and chromatographed using reversed-phase HPLC. Concentration and lyophilization of the purified fractions gave 23 mg (53%) of a yellowish solid. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 486 (M+H).

Example 19

4-(4-Amino-5-*p*-tolyl-4a,7a-dihydro-pyrrolo[2,3-d]pyrimidin-7-yl)-pyridine-2,6-dicarboxylic acid



(a) Pyridine-(2,6-dicarboxylic acid diethyl ester)-4-boronic acid

A mixture of 4-bromopyridine-2,6-dicarboxylic acid diethyl ester (0.10 g, 0.33 mmol), bis(pinacoloto)diboron (0.093 g, 0.36 mmol), [1, 1′-bis(diphenylphosphino)ferrocene]dichloride (5 mol%), potassium acetate (0.097 g, 1.0 mmol) in DMSO (2 mL) was heated to 80 °C for 1 h. Purification by RP HPLC (CH_3CN/H_2O) and lyophylization yielded a white powder (0.07 g, 79%). MS $[M + H]^+$ 268.

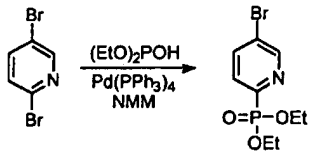
(b) 4-(4-Amino-5-*p*-tolyl-4a,7a-dihydro-pyrrolo[2,3-*d*]pyrimidin-7-yl)-pyridine-2,6-dicarboxylic acid diethyl ester

A mixture of pyridine-(2,6-dicarboxylic acid diethyl ester)-4-boronic acid (0.093 g, 0.27 mmol), 3-*p*-Tolyl-3a,7a-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine (0.03 g, 0.13 mmol mmol), copper(II) acetate (0.048 g, 0.27 mmol) and pyridine (0.3 mL) in DMF (5 mL) were stirred open to the air for 48 h. The mixture was filtered through Celite and the filtrate purified by RP HPLC (CH_3CN/H_2O). Lyophylization yielded a white powder (0.02 g, 34%). MS $[M + H]^+$ 447.

(c) 4-(4-Amino-5-*p*-tolyl-4a,7a-dihydro-pyrrolo[2,3-d]pyrimidin-7-yl)-pyridine-2,6-dicarboxylic acid

To a suspension of 4-(4-amino-5-*p*-tolyl-4a,7a-dihydro-pyrrolo[2,3-*d*]pyrimidin-7-yl)-pyridine-2,6-dicarboxylic acid diethyl ester (0.02 g, 0.036 mmol) in THF (1 mL) and water (1 mL) was added 2N NaOH (1 mL). The mixture was heated at reflux for 1 h at which point HPLC indicated completion. The mixture was acidified with TFA, diluted with DMF (5 mL) and purified by RP HPLC (CH_3CN/H_2O). Lyophylization yielded a white powder (0.01 g, 71%). MS $[M - H]^-$ 389.

G) Embodiments wherein Tb is xxii

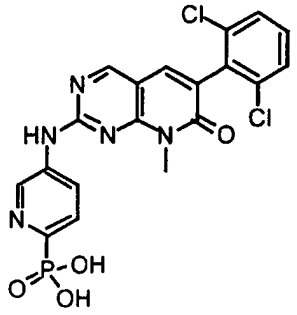


Example 20

Preparation of diethyl 2-(5-bromopyridyl)phosphonate

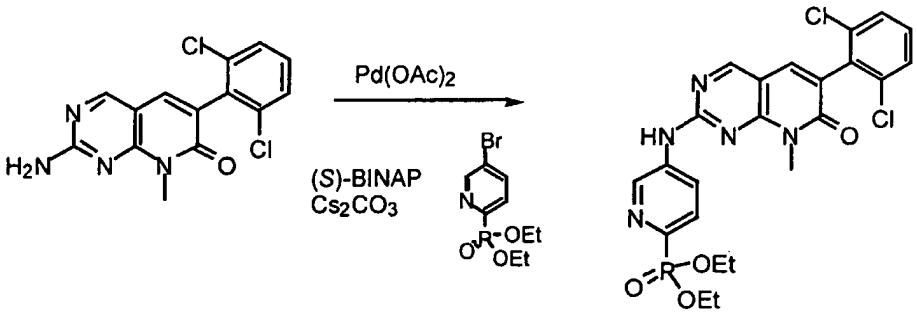
A mixture of 2,5-dibromopyridine (500 mg, 2.11 mmol), NMM (0.46 mL, 4.22 mmol), $(EtO)_2POH$ (0.35 mL, 2.53 mmol) and $Pd(PPh_3)_4$ (122 mg, 0.106 mmol) in CH_3CN was stirred at 80 °C overnight. After cooling, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic extract was then washed with brine, dried over K_2CO_3 and concentrated. The crude material was purified by flash chromatography on silica gel to afford 130 mg (21%) of the desired phosphonate.

{5-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-2-yl}-phosphonic acid



a) {5-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-2-yl}-phosphonic acid diethyl ester

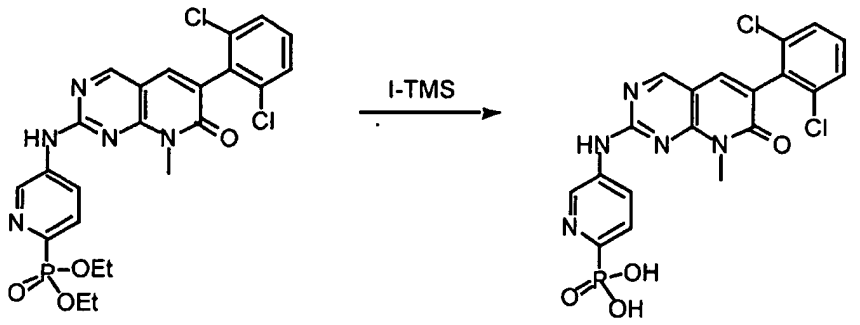
(5-Bromo-pyridin-2-yl)-phosphonic acid diethyl ester



b) (4-bromopyridin-2-yl)-phosphonic acid diethyl ester (64 mg, 0.22 mmol), 2-amino-6-(2,6-dichlorophenyl)pyrido-8-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (70 mg, 0.22 mmol), palladium acetate (5.0 mg, 0.0.023 mmol), (5-bromopyridin-2-yl)-phosphonic acid diethyl ester (64 mg, 0.22 mmol), (*S*)-BINAP (20 mg, 0.032 mmol) and cesium carbonate (141 mg, 0.43 mmol) were placed in toluene (1 mL), flushed with argon, sealed and heated to 95 °C. After 18 h, the reaction was allowed to cool to rt and diluted with H_2O. The mixture was extracted twice with EtOAc and the combined organic extracts washed with brine and dried over Na_2SO_4. The solution was concentrated and chromatographed over silica gel ($CHCl_3$:MeOH,

stepwise gradient 99:1 to 97:3) to give 46 mg (39%) of a yellow solid. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 534 (M+H).

c) {5-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-2-yl}-phosphonic acid



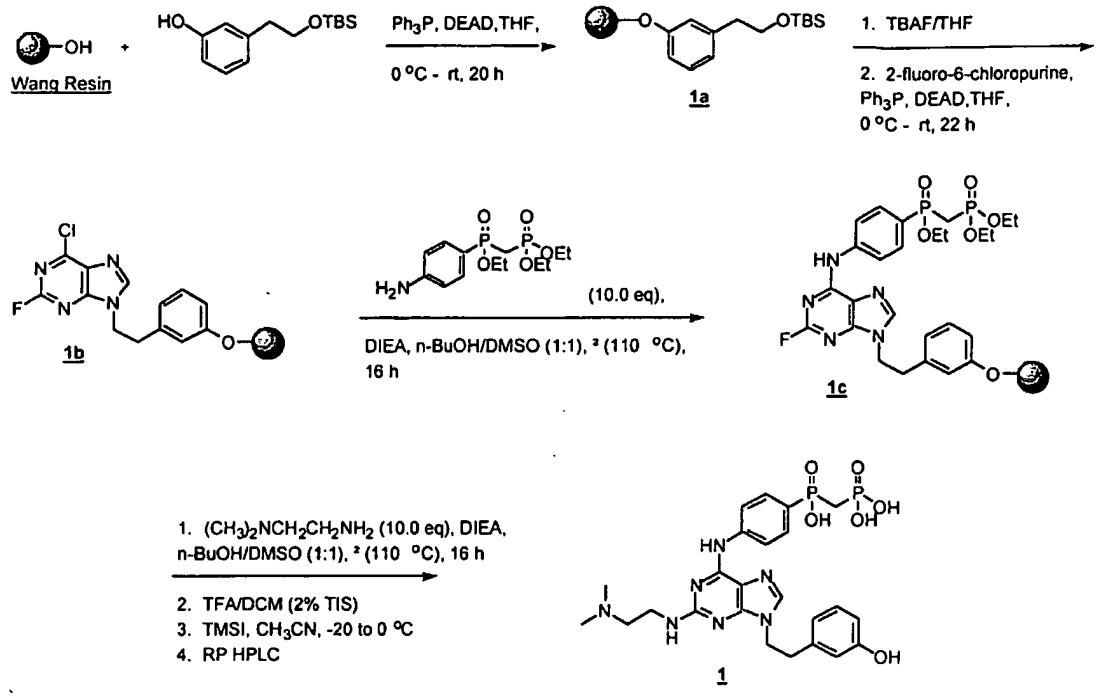
To a cooled solution (0 °C) of {5-[6-(2,6-Dichloro-phenyl)-8-methyl-7-oxo-4a,7,8,8a-tetrahydro-pyrido[2,3-*d*]pyrimidin-2-ylamino]-pyridin-2-yl}-phosphonic acid diethyl ester (46 mg, 0.86 mmol) in MeCN (1.2 mL) was added iodotrimethylsilane (0.3 mL). After 2 h, the reaction was quenched with sodium hydroxide (1 N) and satd sodium thiosulfate. The mixture was filtered and the filtrate chromatographed using reversed-phase HPLC to give 14 mg (34%) of a colorless solid after lyophilization. Electrospray Mass Spectrum (50/50 acetonitrile/water) m/z 534 (M+H).

Example 21

Solid-Phase/Combinatorial Approaches:

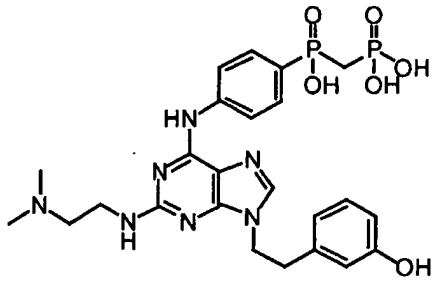
Compounds were synthesized by solid-phase parallel synthesis using a Quest 210 synthesizer (Argonaut Technologies) according to the following scheme for Example 22:

Solid-Phase Parallel Synthesis Scheme



Example 22

(a) [(4-{2-(2-Dimethylamino-ethylamino)-9-[2-(3-hydroxy-phenyl)-ethyl]-9*H*-purin-6-ylamino}-phenyl)-hydroxy-phosphinoylmethyl]-phosphonic acid



(b) 3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-phenol

To a solution of 3-hydroxyphenethyl alcohol (6.0 g, 43.4 mmol) in 275 mL of CH_2Cl_2 was added 6.55 g (43.4 mmol) of TBDMS-Cl (*tert*-butyldimethylsilyl chloride), cooled to 0 °C, then added 7.0 mL (86.8 mmol) of pyridine. The reaction mixture was stirred at ambient temperature overnight. Upon concentration, the crude mixture was purified by silica gel flash chromatography (eluted with hexane then 5% EtOAc/hexane) to provide 8.9 g of a clear oil: ^{1}H NMR (300 MHz, DMSO-d_6)

δ 9.17 (s, 1H), 7.04 (m, 1H), 6.60 (m, 3H), 3.73 (t, J = 6.9 Hz, 2H), 2.65 (t, J = 6.9 Hz, 2H), 0.83 (s, 9H), -0.03 (s, 6H).

(c) Preparation of Ether Resin (1a)

To a Teflon® RV (reaction vessel) containing 0.3 g (0.96 mmol/g, 0.29 mmol) of Wang resin was added a solution of 3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-phenol (0.73 g, 2.9 mmol) and triphenylphosphine (0.38 g, 1.44 mmol) in 1.4 mL of THF. The RV was cooled to 0 °C (Julabo chiller) and then added, under an atmosphere of N_2, 2.0 mL (1.44 mmol) of a 0.72 M solution of DEAD (diethyl azodicarboxylate) in THF. The resin mixture was warmed, while agitating, to ambient temperature over 2 h and then agitated for an additional 20 h, upon which the RV was drained and the resin washed successively with THF (5×5.0 mL), DMA (5×5.0 mL), CH_2Cl_2 (5×5.0 mL), Et_2O (2×5.0 mL), CH_2Cl_2 (1×5.0 mL), Et_2O (1×5.0 mL), and CH_2Cl_2 (2×5.0 mL). Excess solvent was removed via N_2 flow overnight to provide the ether resin **1a**. The following analytical data was obtained upon cleavage of **1a** (3-5 mg) with 30% TFA/CH_2Cl_2 (~5 min): 83% HPLC purity; HPLC RT (retention time, min) matches commercially available 3-hydroxyphenethyl alcohol (TBS group removed in TFA cleavage).

(d) Preparation of Purine Resin (1b)

To the ether resin **1a** (0.29 mmol) was added 6.6 mL (6.57 mmol) of a 1.0 M solution of TBAF (tetrabutylammonium fluoride) in THF. The resin mixture was agitated for 2 h, upon which the RV was drained and the resin washed successively with THF (5×5.0 mL), DMA (5×5.0 mL), CH_2Cl_2 (5×5.0 mL), Et_2O (2×5.0 mL), CH_2Cl_2 (1×5.0 mL), Et_2O (1×5.0 mL), and CH_2Cl_2 (2×5.0 mL). Excess solvent was removed via N_2 flow overnight to provide the deprotected resin. A resin aliquot (3-5 mg) was cleaved with 30% TFA/CH_2Cl_2 (~5 min) to verify resin bound compound integrity: 80% HPLC purity; HPLC RT (retention time, min) matches commercially available 3-hydroxyphenethyl alcohol.

To the dried resin (0.29 mmol) was added a homogeneous suspension of 2-fluoro-6-chloropurine (0.50 g, 2.9 mmol) (for the preparation of 2-fluoro-6-chloropurine see: Gray, N. S.; Kwon, S.; Schultz, P. G. *Tetrahedron Lett.* **1997**, *38*,

1161-1164) and triphenylphosphine (0.38 g, 1.44 mmol) in 1.75 mL of THF. The RV was cooled to 0 °C (Julabo chiller) and then added, under an atmosphere of N_2, 2.0 mL (1.44 mmol) of a 0.72 M solution of DEAD (diethyl azodicarboxylate) in THF. The resin mixture was warmed, while agitating, to ambient temperature over 1.5 h and then agitated for an additional 22 h, upon which the RV was drained and the resin washed successively with THF (5×5.0 mL), DMA (5×5.0 mL), CH_2Cl_2 (5×5.0 mL), Et_2O (2×5.0 mL), CH_2Cl_2 (1×5.0 mL), Et_2O (1×5.0 mL), and CH_2Cl_2 (2×5.0 mL). Excess solvent was removed via N_2 flow overnight to provide the purine resin **1b**. The following analytical data was obtained upon cleavage of **1b** (3-5 mg) with 30% TFA/CH_2Cl_2 (~5 min): 65% HPLC purity, ~5:1 major/minor peaks (no apparent 3-hydroxyphenethyl alcohol HPLC peak).

(e) Preparation of Purine Resin (1c)

To the purine resin **1b** (0.29 mmol) was added a solution of [(4-Amino-phenyl)-ethoxy-phosphinoylmethyl]-phosphonic acid diethyl ester (0.97 g, 2.88 mmol) and N,N-diisopropylethylamine (0.25 mL, 1.44 mmol) in 3.0 mL of 1:1 n-butanol/DMSO. The sealed RV was heated at 110 °C for 16 h, upon which the RV was cooled to ambient temperature, drained, and the resin washed successively with DMA (5×5.0 mL), CH_2Cl_2 (5×5.0 mL), Et_2O (2×5.0 mL), CH_2Cl_2 (1×5.0 mL), Et_2O (1×5.0 mL), and CH_2Cl_2 (2×5.0 mL). Excess solvent was removed via N_2 flow overnight to provide the aminated purine resin **1c**. The following analytical data was obtained upon cleavage of **1c** (3-5 mg) with 30% TFA/CH_2Cl_2 (~5 min): *m/z* 592 (M+H).

(f) [(4-{2-(2-Dimethylamino-ethylamino)-9-[2-(3-hydroxy-phenyl)-ethyl]-9*H*-purin-6-ylamino}-phenyl)-hydroxy-phosphinoylmethyl]-phosphonic acid

To the aminated purine resin **1c** (0.29 mmol) was added a solution of N,N-dimethylethylenediamine (0.25 g, 2.88 mmol) and N,N-diisopropylethylamine (0.25 mL, 1.44 mmol) in 3.0 mL of 1:1 n-butanol/DMSO. The sealed RV was heated at 110 °C for 16 h, upon which the heat was turned off, the RV drained immediately, and the resin washed (while still hot) successively with DMA (5×5.0 mL), CH_2Cl_2 (5×5.0 mL, at ambient temperature), Et_2O (2×5.0 mL), CH_2Cl_2 (1×5.0 mL), Et_2O (1×5.0

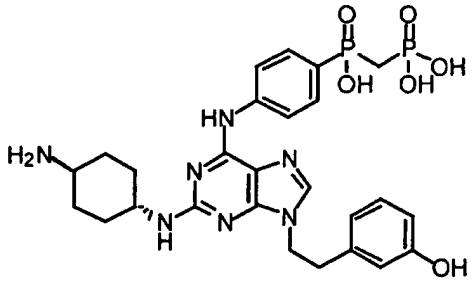
mL), and CH_2Cl_2 (2×5.0 mL). Excess solvent was removed via N_2 flow overnight to provide the bis-aminated purine resin.

To the bis-aminated purine resin (0.29 mmol) was added 5.6 mL of 30% TFA/ CH_2Cl_2 (2 % triisopropyl silane). The resin mixture was agitated for 1 h, upon which the filtrate was collected and the resin washed with CH_2Cl_2 (3×5.0 mL). The combined filtrates were concentrated (Savant speed-vac), added 3-4 mL CH_2Cl_2, then reconcentrated to provide a dark yellow oil.

The oil was dissolved in 6.6 mL of CH_3CN, cooled to 0 °C, then added 1.0 mL (7.2 mmol) of TMSI (iodotrimethylsilane). The resulting yellow solution (some precipitate) was stored at -20 °C for 2 h (periodic swirling), then 0 °C for 1 h, upon which 0.4 mL (2.81 mmol) of TMSI was added and reaction continued at 0 °C for 3 h. The excess TMSI was quenched at 0 °C with ~4 mL of 20% aqueous $NaHSO_3$, the pH adjusted to 11-12 with 10% NaOH, and the CH_3CN removed by rotary evaporation. The pH was re-adjusted to 10-11 with TFA, upon which the solution was filtered (0.2 μm, PTFE filter) and purified by RP-HPLC (CH_3CN/H_2O). Lyophilization provided a white solid isolated as its TFA salt (0.035 g): ^1H NMR (300 MHz, DMSO-d_6) δ 9.76 (s, 1H), 9.33 (br s, 1H), 8.07-7.65 (m, 5H), 7.08-6.59 (m, 5H), 4.27 (m, 2H), 3.66 (m, 2H), 3.32 (m, 2H), 3.04 (m, 2H), 2.85 (s, 6H), 2.37 (m, 2H); *m/z* 576 (M+H).

Example 23

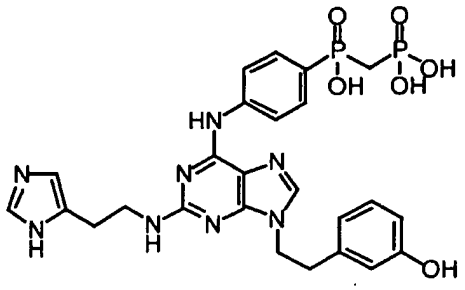
[(4-{2-(*trans*-4-Amino-cyclohexylamino)-9-[2-(3-hydroxy-phenyl)-ethyl]-9*H*-purin-6-ylamino}-phenyl)-hydroxy-phosphinoylmethyl]-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The white solid was isolated as a TFA salt: *m/z* 602 (M+H)

Example 24

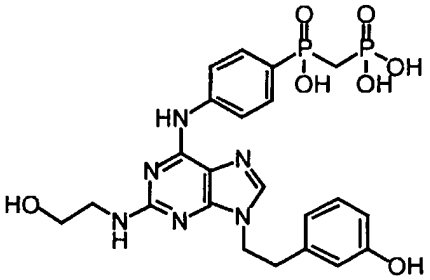
[Hydroxy-(4-{9-[2-(3-hydroxy-phenyl)-ethyl]-2-[2-(3*H*-imidazol-4-yl)-ethylamino]-9*H*-purin-6-ylamino}-phenyl)-phosphinoylmethyl]-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The white solid was isolated as a TFA salt: *m/z* 599 (M+H)

Example 25

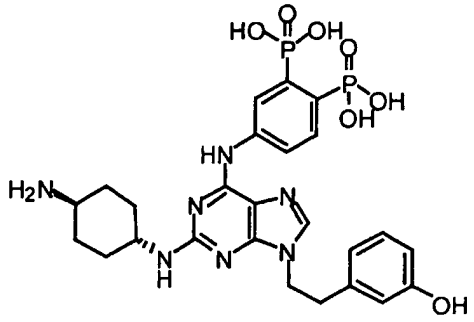
[Hydroxy-(4-{2-(2-hydroxy-ethylamino)-9-[2-(3-hydroxy-phenyl)-ethyl]-9*H*-purin-6-ylamino}-phenyl)-phosphinoylmethyl]-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The product was isolated as a white solid: *m/z* 549 (M+H)

Example 26

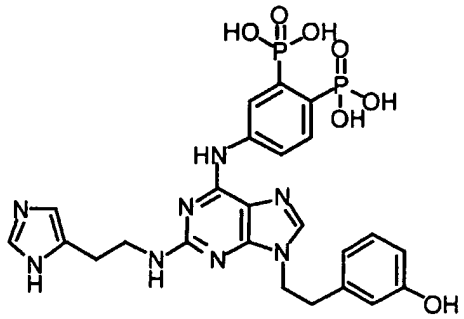
(5-{2-(*trans*-4-Amino-cyclohexylamino)-9-[2-(3-hydroxy-phenyl)-ethyl]-9*H*-purin-6-ylamino}-2-phosphono-phenyl)-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The white solid was isolated as a TFA salt: *m/z* 604 (M+H)

Example 27

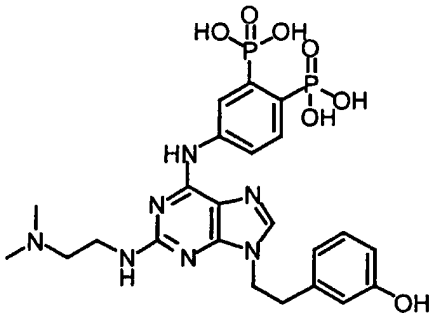
(5-{9-[2-(3-Hydroxy-phenyl)-ethyl]-2-[2-(3*H*-imidazol-4-yl)-ethylamino]-9*H*-purin-6-ylamino}-2-phosphono-phenyl)-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The white solid was isolated as a TFA salt: *m/z* 601 (M+H)

Example 28

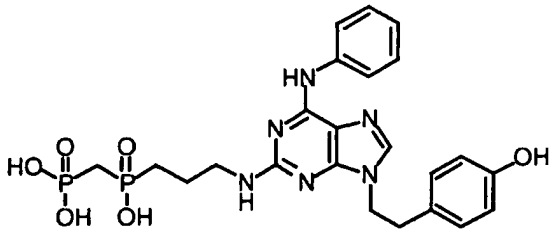
(5-{2-(2-Dimethylamino-ethylamino)-9-[2-(3-hydroxy-phenyl)-ethyl]-9*H*-purin-6-ylamino}-2-phosphono-phenyl)-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The product was obtained as a white solid: *m/z* 578 (M+H)

Example 29

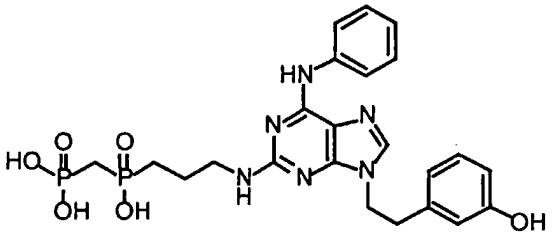
[Hydroxy-(3-{9-[2-(4-hydroxy-phenyl)-ethyl]-6-phenylamino-9*H*-purin-2-ylamino}-propyl)-phosphinoylmethyl]-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The product was obtained as a white solid: *m/z* 547 (M+H)

Example 30

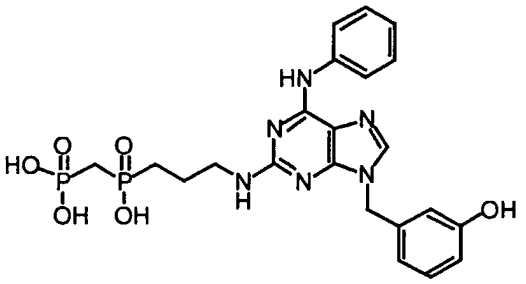
[Hydroxy-(3-{9-[2-(3-hydroxy-phenyl)-ethyl]-6-phenylamino-9*H*-purin-2-ylamino}-propyl)-phosphinoylmethyl]-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The product was obtained as a white solid: *m/z* 547 (M+H)

Example 31

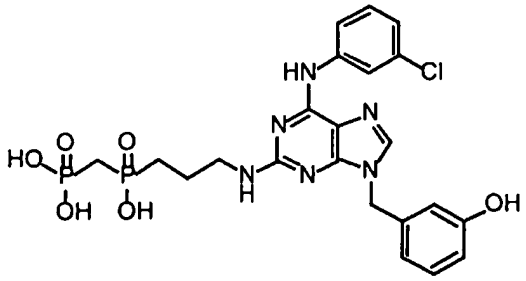
(Hydroxy-{3-[9-(3-hydroxy-benzyl)-6-phenylamino-9*H*-purin-2-ylamino]-propyl}-phosphinoylmethyl)-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The product was obtained as a white solid: *m/z* 533 (M+H)

Example 32

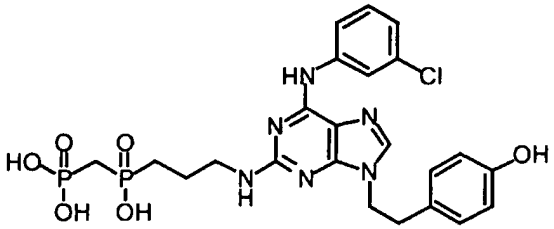
({3-[6-(3-Chloro-phenylamino)-9-(3-hydroxy-benzyl)-9*H* -purin-2-ylamino]-propyl}-hydroxy-phosphinoylmethyl)-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The product was obtained as a white solid: *m/z* 567 (M+H)

Example 33

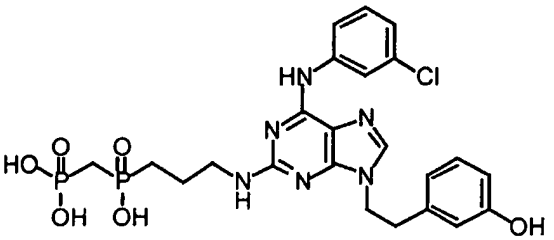
[(3-{6-(3-Chloro-phenylamino)-9-[2-(4-hydroxy-phenyl)-ethyl]-9*H* -purin-2-ylamino}-propyl)-hydroxy-phosphinoylmethyl]-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The product was obtained as a white solid: *m/z* 581 (M+H)

Example 34

[(3-{6-(3-Chloro-phenylamino)-9-[2-(3-hydroxy-phenyl)-ethyl]-9*H* -purin-2-ylamino}-propyl)-hydroxy-phosphinoylmethyl]-phosphonic acid



The title compound was synthesized in a manner similar to that described for Example 22. The product was obtained as a white solid: *m/z* 581 (M+H)

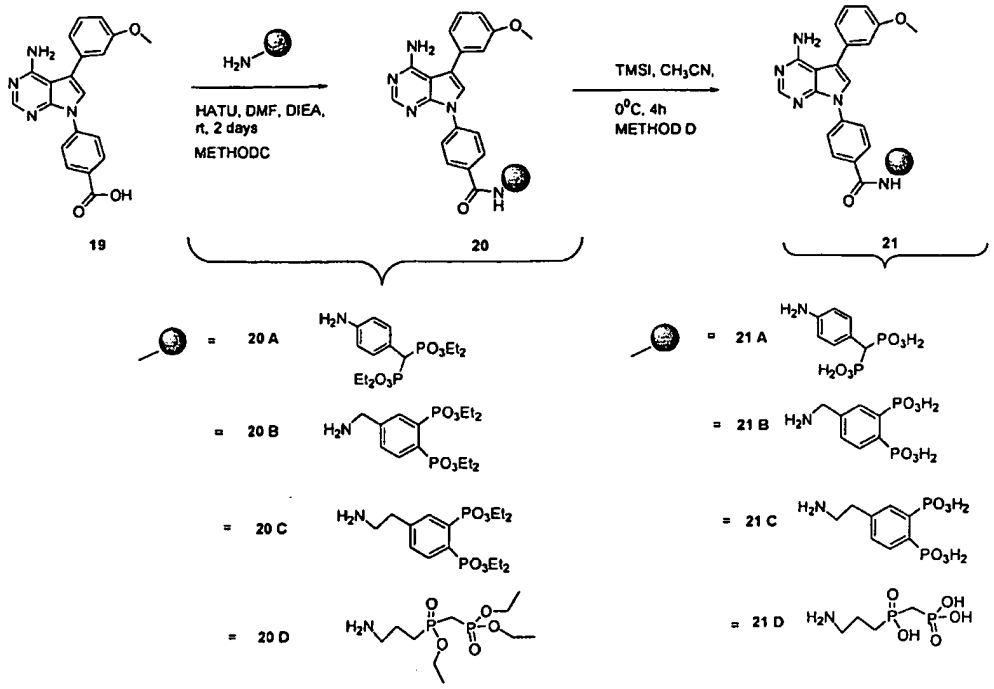
Example 35

The above techniques can also be applied to typical, solution-phase combinatorial synthesis. As described below, a library of compound were rapidly prepared by coupling bone-targeting moieties with payload fragments.

Synthesis of bone-targeting analogs of 4-amino-5-(3-methoxyphenyl)-7-(4-carboxy phenyl)pyrrolo[2,3-d]-pyrimidine

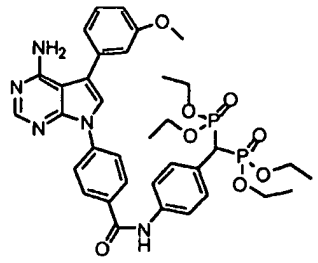
These analogs 21A-21D were synthesized according to Scheme 6 starting from the 4-amino-5-(3-methoxyphenyl)-7-(4-carboxyphenyl)pyrrolo[2,3-d]-pyrimidine.

Scheme 6



Method C:

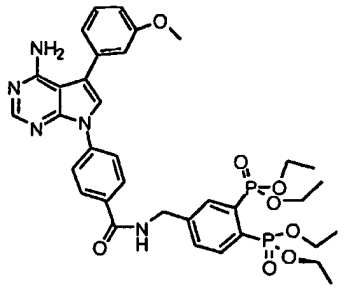
Carboxylic acid (0.25 mmol) 19/22 was taken up in DMF (5 mL) and cooled in ice. HATU (0.5 mmol) was then added followed by the bone-targeting amines A-D and ethyl diisopropyl amine (0.5 mmol). The reaction mixture was stirred at ambient temp. for 2 days. DMF was removed in vacuo and the residue was taken up in ethyl acetate. Ethyl acetate layer was washed with sodium bicarbonate (10%) followed by 10% citric acid and then water. Organic extract was dried over sodium sulphate and concentrated and purified by chromatography using methylene chloride/methanol (5 - 10%).



20A

4-amino-5-(3-methoxyphenyl)-7-{4-[N-(4-bisdiethylphosphonomethyl)phenyl] carboxamido)}pyrrolo[2,3-d]-pyrimidine 20A:

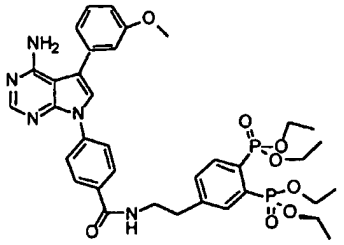
Prepared from 19 as a pale yellow gum. MS: 720 (M-H), 744 (M+23).



20B

4-amino-5-(3-methoxyphenyl)-7-{4-[N-(3,4-bisdiethylphosphono phenyl) methyl] carboxamido)}pyrrolo[2,3-d]-pyrimidine 20B:

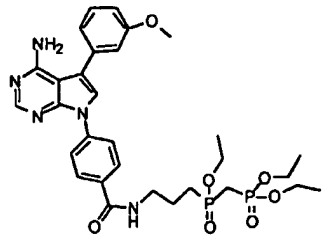
Prepared from 19 as a pale yellow gum. MS: 720 (M-H).



20C

4-amino-5-(3-methoxyphenyl)-7-{4-[N-(2-(3,4-bisdiethylphosphonophenyl)ethyl)] carboxamido)}pyrrolo[2,3-d]-pyrimidine 20C:

Prepared from 19 as a pale yellow gum. MS: 734 (M-H), 768(M+23)



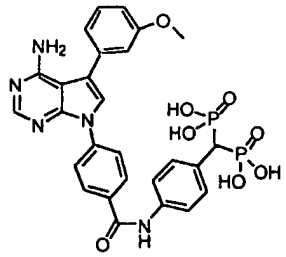
20D

4-amino-5-(3-methoxyphenyl)-7-{4-[N-3-triethyl bisphosphono - methylenepropyl]phenyl}carboxamido)}pyrrolo[2,3-d]-pyrimidine 20D

Prepared from 19 as a pale yellow gum. MS: 642 (M-H).

Method D :

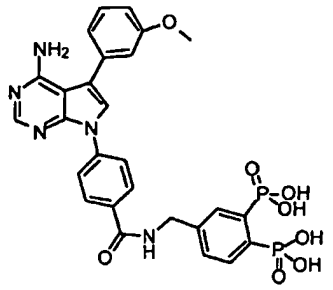
To a cooled (-20 °C) solution of the phosphonate esters 20A-D (0.2 mmol) in acetonitrile (5 mL) was added TMSI (2 mmol) and stirred at 0 °C for 4.5h after which time it was quenched with sodium bicarbonate solution followed by a 10% solution of sodium bisulphite until the color of iodine is dissipated. The aqueous layer was washed with ethyl acetate and purified by Preparative HPLC.



21A

4-amino-5-(3-methoxyphenyl)-7-{4-[N-(4-bisphosphono methyl)phenyl] carboxamido)}pyrrolo[2,3-d]-pyrimidine 21A:

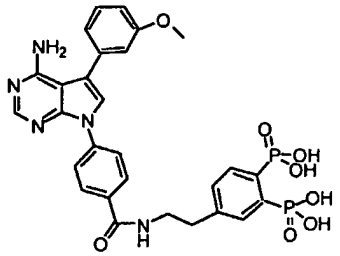
Prepared from 20A using Method D as a white solid. MS: 608 (M-H), 610 (M+H).



21B

4-amino-5-(3-methoxyphenyl)-7-{4-[N-(3,4-bisphosphono phenyl) methyl] carboxamido)}pyrrolo[2,3-d]-pyrimidine 21B:

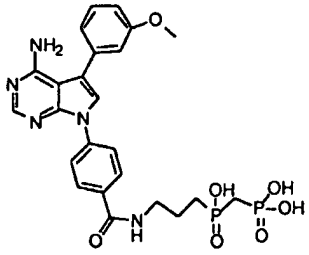
Prepared from 20B using Method D as a white solid. MS: 608 (M-H), 610 (M+H).



21C

4-amino-5-(3-methoxyphenyl)-7-{4-[N-(2-(3,4-bisphosphono phenyl)ethyl)] carboxamido)}pyrrolo[2,3-d]-pyrimidine 21C:

Prepared from 20C using Method D as a white solid. MS: 622 (M-H), 646 (M+23).



21D

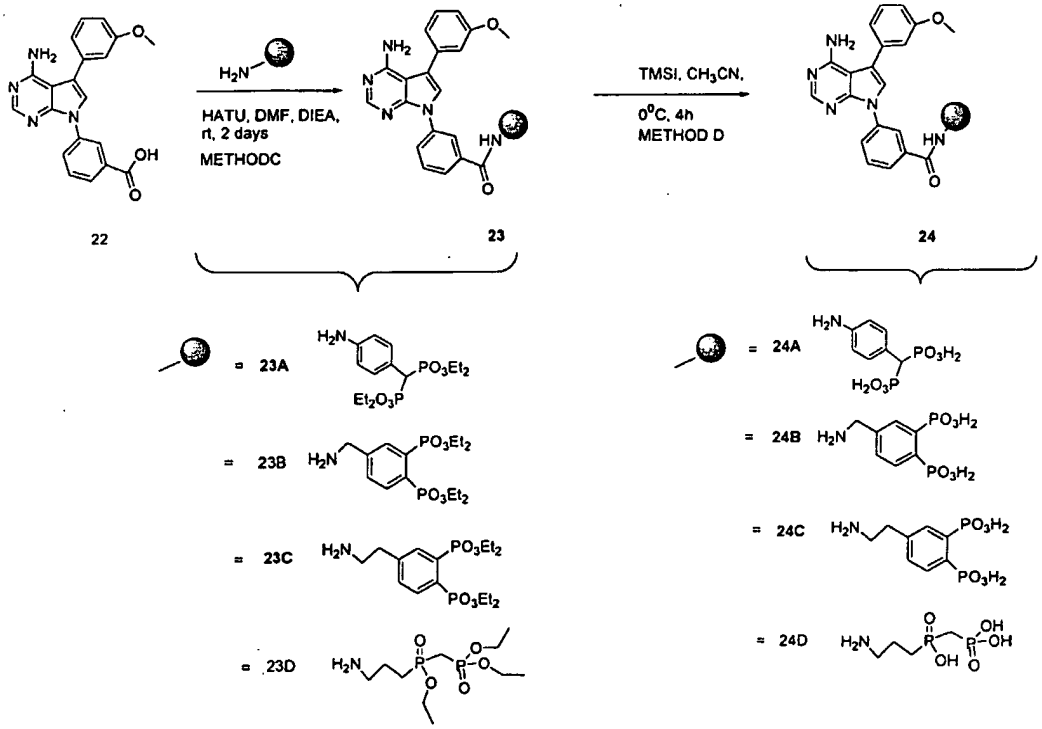
4-amino-5-(3-methoxyphenyl)-7-{4-[N-3-bisphosphonomethylene propyl]phenyl}carboxamido)}pyrrolo[2,3-d]-pyrimidine 21D:

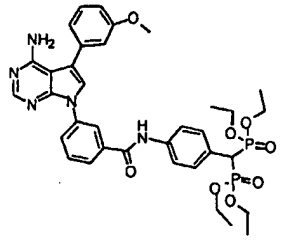
Prepared from 20D using Method D as a white solid. MS: 558 (M-H).

Synthesis of bone-targeting analogs of 4-amino-5-(3-methoxyphenyl)-7-(3-carboxyphenyl)pyrrolo[2,3-d]-pyrimidine

These analogs 24A-24D were synthesized according to Scheme 7 starting from the 4-amino-5-(3-methoxyphenyl)-7-(3-carboxyphenyl)pyrrolo[2,3-d]-pyrimidine.

Scheme 7

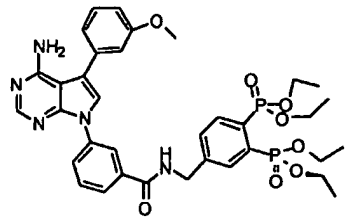




23A

4-amino-5-(3-methoxyphenyl)-7-{3-[N-(4-bisdiethylphosphonomethyl)phenyl] carboxamido)}pyrrolo[2,3-d]-pyrimidine 23A:

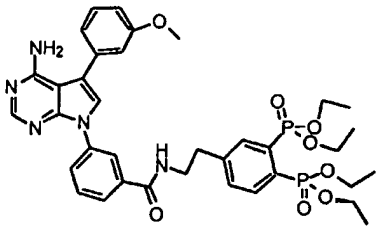
Prepared from 22 as a pale yellow gum using Method C. MS: 720 (M-H), 744 (M+23).



23B

4-amino-5-(3-methoxyphenyl)-7-{3-[N-(3,4-bisdiethylphosphono phenyl) methyl] carboxamido)}pyrrolo[2,3-d]-pyrimidine 23B:

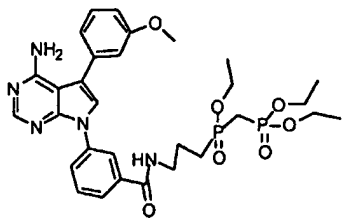
Prepared from 22 as a pale yellow gum using Method C. MS: 720 (M-H).



23C

4-amino-5-(3-methoxyphenyl)-7-{3-[N-(2-(3,4-bisdiethylphosphonophenyl) ethyl)] carboxamido)}pyrrolo[2,3-d]-pyrimidine 23C:

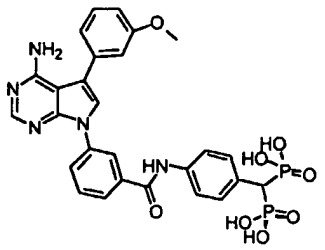
Prepared from 22 as a pale yellow gum using Method C. MS: 734 (M-H), 768 (M+23).



23D

4-amino-5-(3-methoxyphenyl)-7-{4-[N-3-triethyl bisphosphono -methyleneprop yl]phenyl}carboxamido)}pyrrolo[2,3-d]-pyrimidine 23D

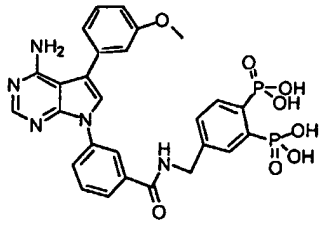
Prepared from 22 as a pale yellow gum. MS: 642 (M-H).



24A

4-amino-5-(3-methoxyphenyl)-7-{3-[N-(4-bisphosphono methyl)phenyl] carboxamido)}pyrrolo[2,3-d]-pyrimidine 24A:

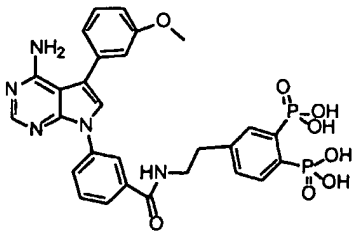
Prepared from 23A using Method D as a white solid. MS : 608 (M-H), 610 (M+H).



24B

4-amino-5-(3-methoxyphenyl)-7-{3-[N-(3,4-bisphosphono phenyl)methyl] carboxamido)}pyrrolo[2,3-d]-pyrimidine 24B:

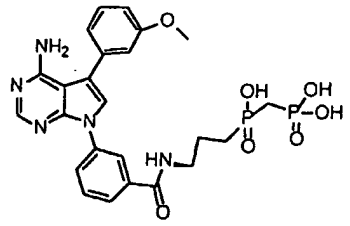
Prepared from 23B using Method D as a white solid. MS : 608 (M-H), 610 (M+H).



24C

4-amino-5-(3-methoxyphenyl)-7-{3-[N-(2-(3,4-bisphosphono phenyl)ethyl)] carboxamido)}pyrrolo[2,3-d]-pyrimidine 24C:

Prepared from 23C using Method D as a white solid. MS: 622 (M-H), 646 (M+23).

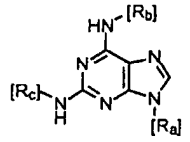


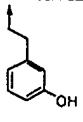
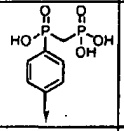
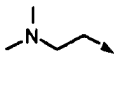
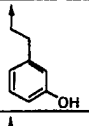
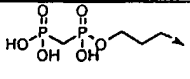
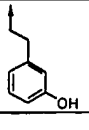
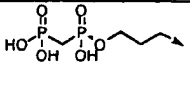
24D

4-amino-5-(3-methoxyphenyl)-7-{3-[N-3-bisphosphonomethylene propyl]phenyl}carboxamido)}pyrrolo[2,3-d]-pyrimidine 24D:

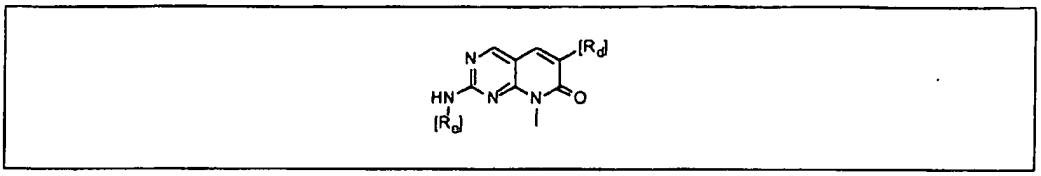
Prepared from 23D using Method D as a white solid. MS: 558 (M-H).

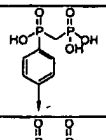
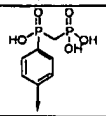
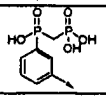
BONE-TARGETED PURINE SERIES



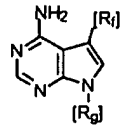
Example #	R_a	R_b	R_c	Src Kinase Inhibition IC50 (μM)	Anti-Resorption Cell Assay % Inhib (μM)
22					75 @ 20
30		Ph		0.055	100 @ 20
34		3-ClPh		0.12	50-70 @ 4

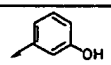
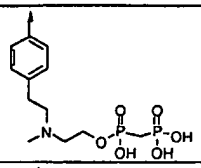
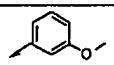
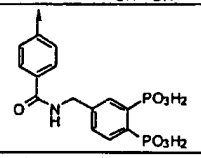
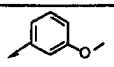
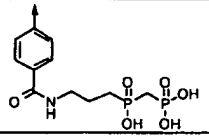
BONE-TARGETED AMINOPYRIDOPYRIMIDINONES SERIES



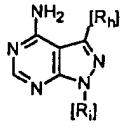
Example #	Rd	Re	Src Kinase Inhibition IC50 (μM)	Anti-Resorption Cell Assay % Inhib (μM)
i-A			0.002	50 @ 4
i-B			0.008	75-90 @ 20
i-C			0.12	100 @ 20

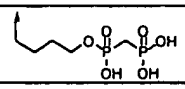
BONE-TARGETED PYRROLOPYRIMIDINE SERIES



Example #	Rf	Rg	Src Kinase Inhibition IC50 (μM)	Anti-Resorption Cell Assay % Inhib (μM)
14			0.004	25-50 @ 4
21B			0.87	50 @ 4
21D			0.13	

BONE-TARGETED PYRRAZOLOPYRIMIDINE SERIES



Example #	Rh	Ri	Src Kinase Inhibition IC50 (μM)	Anti-Resorption Cell Assay % Inhib (μM)
13			29	50 @ 3

Assays

1. Anti-Resorption Cell Assay (Rabbit Osteoclast):

Femurs, tibias, and scapulas were isolated from 3-4 day old New Zealand white rabbits (Millbrook Farms, Amherst, MA). Bones were chopped and minced in a-MEM (Gibco-BRL) containing 0.55 g/L $NaHCO_3$, 10 mM HEPES (Gibco-BRL), 50 units/ml penicillin, and 0.05 mg/ml streptomycin, pH 7.1. Bone fragments were allowed to settle by gravitation, supernatant was collected and centrifuged at 400 RPM (Beckman GS-6KR) for two minutes, and the cell pellet was resuspended in the same medium supplemented with 10% HIFBS (Hyclone). For prebinding experiments, 0.75 ml of cell suspension was added to wells containing sperm whale dentine discs preincubated for 2 hours with 0.75 ml culture medium containing a 2X concentration of test compound. Alternatively, 0.75 ml of cell suspension was added to each well containing dentine slices preincubated with 0.75 ml culture medium alone and test compound was added after the adhesion phase. Sperm whale dentine was cut as 1 mm x 6 mm circular discs. The adhesion phase was carried out for 30 minutes at 37 °C and 5% CO_2 and then the medium and non-adherent cells and debris were removed by aspiration. Fresh culture medium containing serially diluted test compounds was added and cells were incubated on dentine for 24 hours at 37 °C and 5% CO_2. After the resorption phase, dentine slices were soaked for 30 seconds in 0.5% sodium hypochlorite, wiped clean of adherent cells, and then stained for 30-45 seconds with 1% toluidine blue. Resorption was measured using reflective light microscopy and automated image analysis. The resorbed area was measured on the entire 6 mm disc. Remaining cells in the 24-well plates were stained for tartrate resistant acid phosphatase (TRAP) and also assessed visually for the presence of fibroblasts. Experiments were carried out containing triplicate samples for each concentration of compound tested with five untreated control samples per plate. IC_{50} values were calculated based on the % resorption in the presence of compound relative to vehicle alone treated control samples. Data were calculated from at least three independent experiments each containing triplicate samples.

2. Src Kinase Inhibition Assay:

Compounds were tested for their ability to inhibit Src kinase using the scintillation proximity assay (SPA) technology as developed by Amersham. Reagents include: Streptavidin SPA beads from Amersham, 2-[N-morpholino]ethanesulfonic acid from Sigma, ATP from Boerhinger Mannheim, [^{33}P]ATP : from NEN (NEG 602H), the substrate - biotinylated peptide substrate 1 (PKS1) (cdc2 peptide) from Pierce which is prepared at 12.5 μM (5X solution) in kinase buffer, and the enzyme, human recombinant c-Src at 135 μg/ml (stock solution) which is diluted 1/40 in kinase buffer (3.38 μg/ml) before use. Buffers include: (a) Kinase buffer which contains MES 30 mM pH 6.8, $MgCl_2$ 10 mM, Orthovanadate 0.25 mM, PMSF 0.1 mM, and DTT 1mM; (b) ATP buffer which contains ATP 5 mM in $MgCl_2$ 50 mM buffer (stock solution). Note that before each use dilute in MES to 100 μM (5X solution) add 100 μCi/mL [^{33}P]ATP; and (c) PBS Stop buffer which contains ATP 0.1 mM, EDTA 40 mM, Triton 0.1%. Streptavidin beads are suspended at 3.3 mg/ml in stop buffer and mixed by shaking. The Kinase reaction proceeds by stepwise addition to wells on the 96 well-plate of the following: (a) 10 μL kinase buffer + 10% DMSO or compound to be tested at different concentration in MES + 10 % DMSO, (b) 10 μL kinase buffer, (c) 10 μL substrate 12.5 μM, (d) 10 μL enzyme 3.38 μg/ml, and (e) 10 μL ATP 100 μM containing 0.2 μCi [^{33}P]ATP. Incubation for 2 hours at 30 degrees C is followed by addition of 150 μL Stop buffer containing 500 μg streptavidin beads. Incubation proceeds for 30 min at room temperature, followed by centrifugation for 5 min at 2000 rpm, and reading on a Wallac Microbeta Scintillation counter.

3. Hydroxyapatite Assay:

Hydroxyapatite is the principal mineral component of bone. Hydroxyapatite adsorption chromatography is used as an assay to evaluate the bone-targeting potential of both individual bone-targeting moieties ("monomers") and of pharmaceuticals incorporating bone-targeting groups.

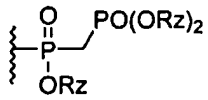
Method: The rentention time of a test compound is measured using a linear gradient from 10 mM sodium phosphate, 0.15 N NaCl, pH = 6.8 to 500 mM sodium phosphate, 0.15 N NaCl, pH = -6.8 on a TSK-Gel HA 1000 high pressure liquid chromatography column (7.5 mm x 75 mm). The rentention time of the compound is expressed in terms of K = (retention time-void time)/void. This K value is corrected

using two reference compounds to correct from inter-column and inter-system variation to obtain a K' value.

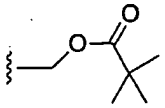
Reference Compounds: K' values were determined for known bone targeted compounds, the bisphosphonate, alendronate and tetracycline. Alendronate gave a K' value of 3.7 and tetracycline gave a K' value of 2.0.

Example 36

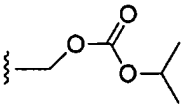
As described previously, the compounds of the present invention may be provided as pro-drugs. To give but one example, bone targeting moieities of the following formula:



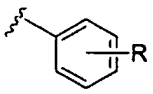
may be protected using the following R_Z groups:



Atack, J. R. et al. *J. of Pharmacology and Experimental Therapeutics* **1994**, *270*, 70.



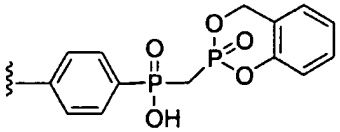
Arimilli, M. N., et al. *Antiviral Chemistry & Chemotherapy* **1997**, *8*, 557.



Serafinowska, H. T., et el. *J. Med. Chem.* **1995**, *35*, 1372.

Ahlmark, M., *J. Med. Chem.* **1999**, *42*, 1473.

Alternatively, the bone targeting moiety may be provided as a pro-drug with the formula:



Meier, C., et al. *J. Med. Chem.* **1998**, *41*, 1417.

5 For a review of pro-drugs such as these, please see Krise, J. P., Stella, V. J. *Advanced Drug Delivery Reviews* **1996**, 19:287; incorporated herein by reference.

Claims

We claim:

1. A compound having the general formula **(I)**:

Hc-X-K-Cy-L-Z-Tb

(I)

wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

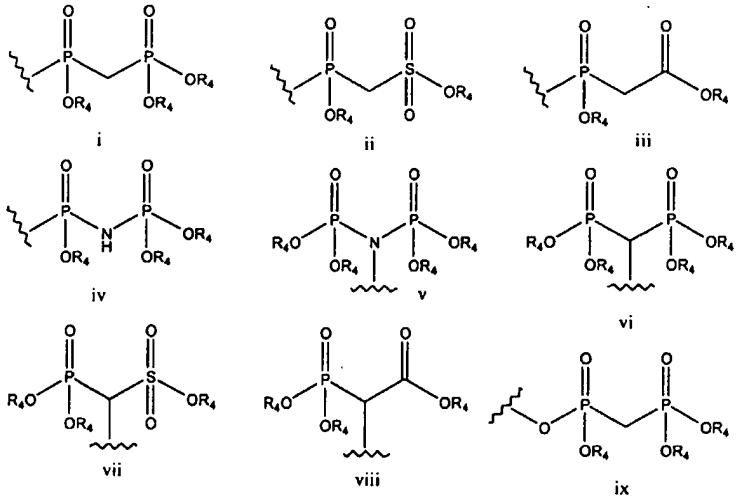
R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

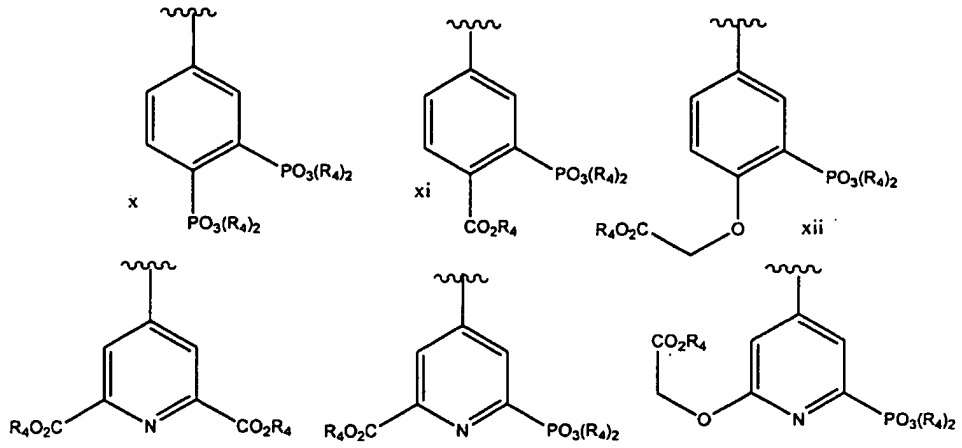
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

Tb represents a bone-targeting group selected from:





and R_4, independently for each occurrence, represents H or lower alkyl,

wherein Hc-X-K-Cy-L is free of hydrolyzable linkages.

2. A compound having the general formula **(II)**: Hc-X-K-Z-Tb, wherein

K is absent or represents $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

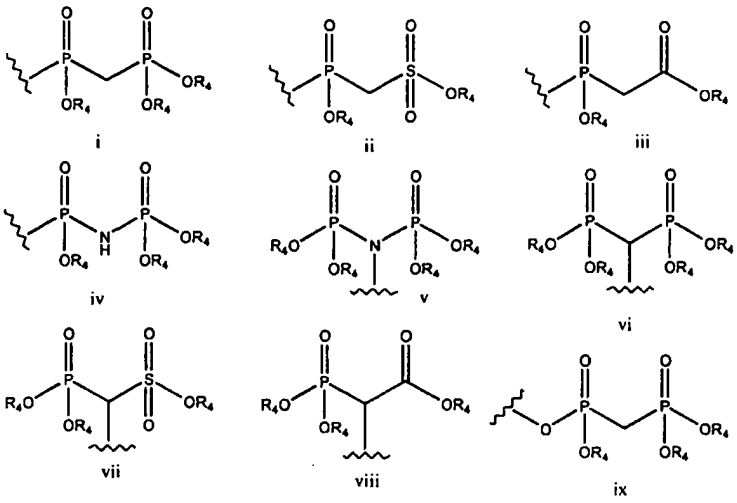
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethylene or ethyne;

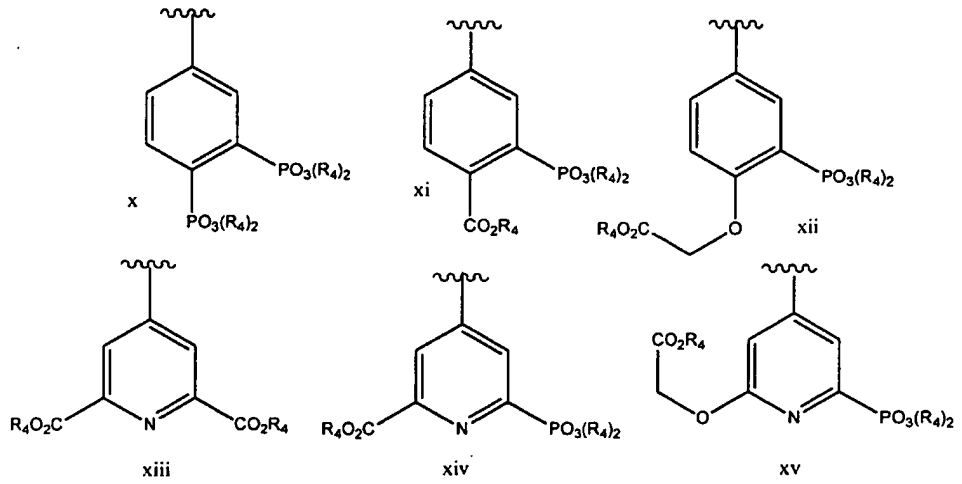
p and n, independently, represent integers from 0-10.

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl.

Hc represents a heterocycle;

Tb represents a bone-targeting group selected from:





and R_4, independently for each occurrence, represents H or lower alkyl, wherein Hc-X-K is free of hydrolyzable linkages.

3. The compound of claim 1 or 2, wherein the compound selectively targets osteoclasts.

4. The compound of claim 1 or 2, wherein R_4 represents H for all occurrences.

5. The compound of claim 1, wherein Cy represents an uncharged carbocycle or nitrogen-bearing heterocycle.

6. The compound of claim 1, wherein Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system having between 8 and 11 atoms.

7. The compound of claim 1, wherein Cy represents phenyl.

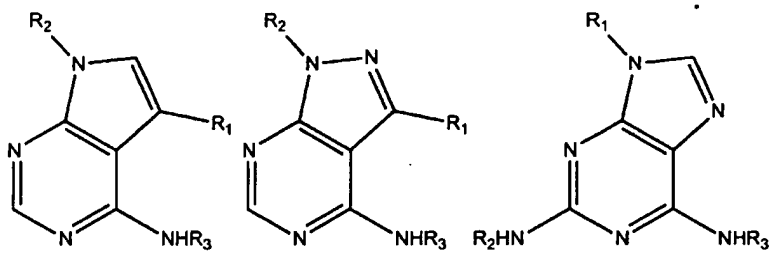
8. The compound of claim 1, wherein Cy represents a bicyclic ring system, whereof L is attached to a first ring and K is attached to a second ring.

9. The compound of claim 1 or 2, wherein Hc represents a bicyclic structure.

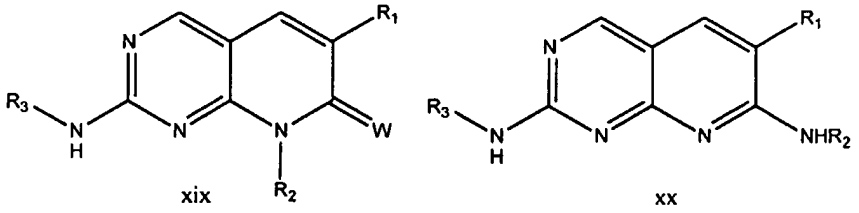
10. The compound of claim 9, wherein the two rings of the bicyclic structure consist of carbon and nitrogen atoms.

11. The compound of claim 1 or 2, wherein K is directly attached to a heteroatom of Hc.

12. The compound of claim 1 or 2, wherein Hc is selected from:



xvi xvii xviii



xix xx

wherein one of R_1, R_2, and R_3 represents a bond to K, the others represent, independently, hydrogen, halogen, alkyl, aralkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, cycloalkyl, polycyclyl, alkyl alkenyl, alkyl alkynyl, or alkanoyl, or taken

together with the nitrogen to which it is attached, represent amidine, amide, carbamate, urea, or guanidine; and

W represents O or S.

13. The compound of claim 1, wherein Tb is represented by i and Z is absent.

14. The compound of claim 13, wherein L is absent.

15. The compound of claim 1 or 2, wherein Tb is selected from xi, xii, xiv, and xv.

16. The compound of claim 1 or 2, wherein Tb is selected from v, vii, and viii.

17. The compound of claim 1 or 2, wherein Tb is selected from ii, iii, or iv.

18. The compound of claim 1 or 2, wherein Tb is represented by x.

19. The compound of claim 1 or 2, wherein Tb is represented by ix.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

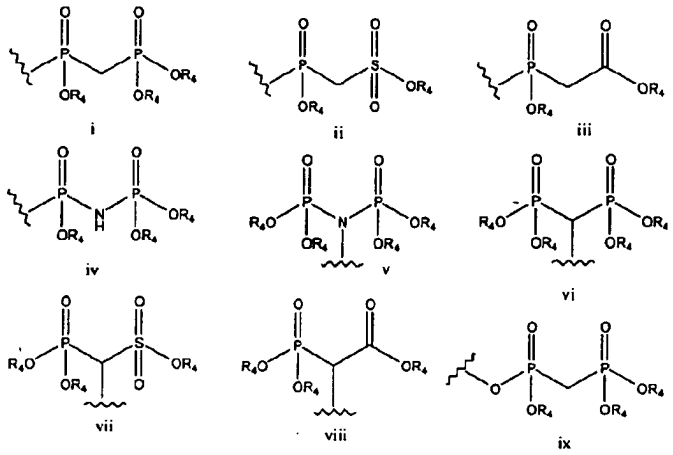
R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

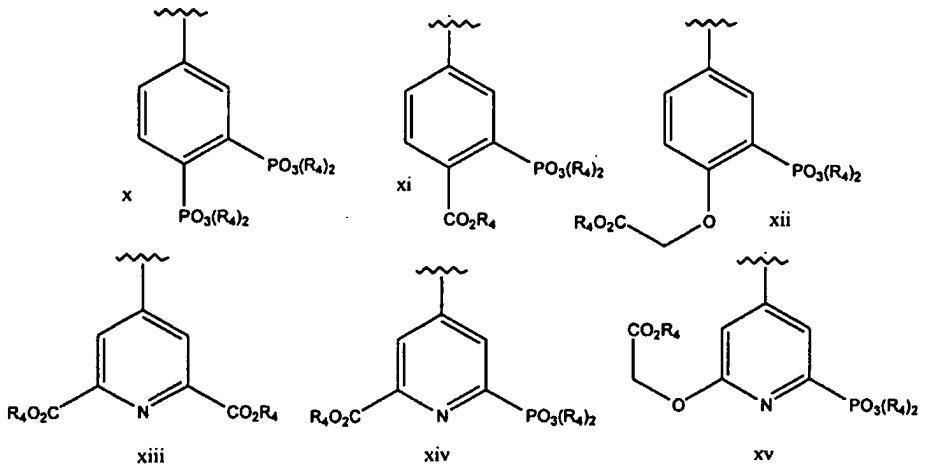
p and n, independently, represent integers from 0-10;

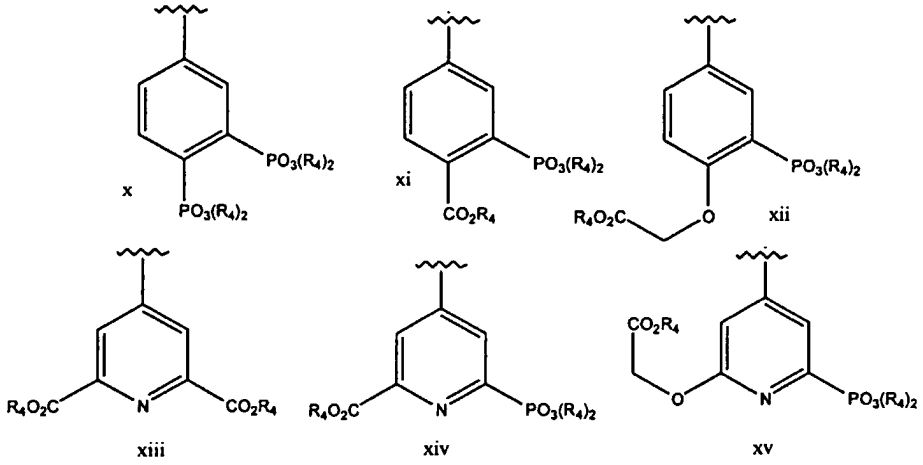
Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

Tb represents a bone-targeting group selected from:







and R_4, independently for each occurrence, represents H or lower alkyl,

wherein Hc-X-K is free of hydrolyzable linkages.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the general formula **(II)**: Hc-X-K-Z-Tb, wherein

K is absent or represents $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

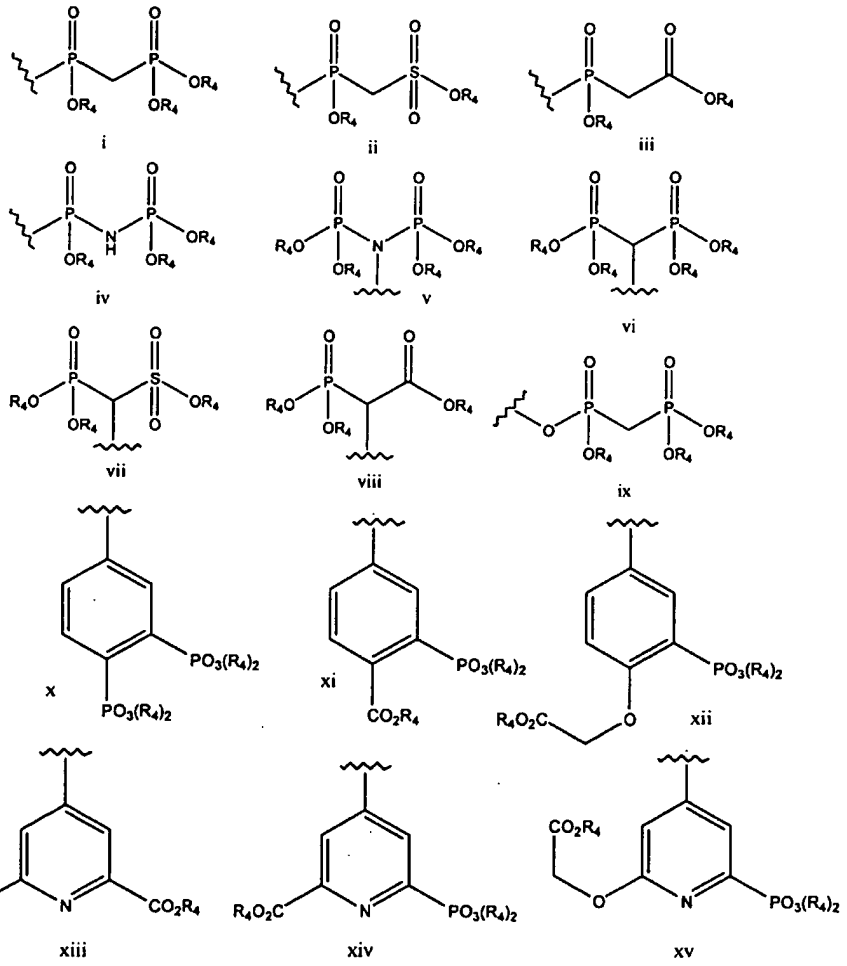
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethylene or ethyne;

p and n, independently, represent integers from 0-10.

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl.

Hc represents a heterocycle;

Tb represents a bone-targeting group selected from:



and R_4, independently for each occurrence, represents H or lower alkyl, wherein Hc-X-K-Cy-L is free of hydrolyzable linkages.

22. The pharmaceutical composition of claim 20 or 21, wherein the compound selectively targets osteoclasts.

23. The pharmaceutical composition of claim 20 or 21, wherein R_4 represents H for all occurrences.

24. The pharmaceutical composition of claim 20, wherein Cy represents an uncharged carbocycle or nitrogen-bearing heterocycle.

25. The pharmaceutical composition of claim 20, wherein Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system having between 8 and 11 atoms.

26. The pharmaceutical composition of claim 20, wherein Cy represents phenyl.

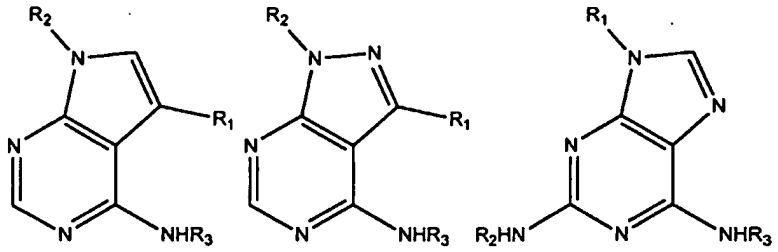
27. The pharmaceutical composition of claim 20, wherein Cy represents a bicyclic ring system, whereof L is attached to a first ring and K is attached to a second ring.

28. The pharmaceutical composition of claim 20 or 21, wherein Hc represents a bicyclic structure.

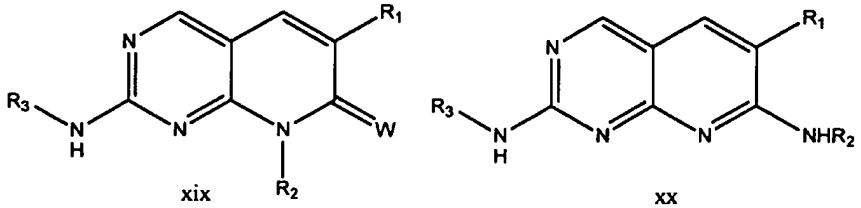
29. The pharmaceutical composition of claim 20 or 21, wherein the two rings of the bicyclic structure consist of carbon and nitrogen atoms.

30. The pharmaceutical composition of claim 20 or 21, wherein K is directly attached to a heteroatom of Hc.

31. The pharmaceutical composition of claim 20 or 21, wherein Hc is selected from:



xvi xvii xviii



xix xx

wherein one of R_1, R_2, and R_3 represents a bond to K, the others represent, independently, hydrogen, halogen, alkyl, aralkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, cycloalkyl, polycyclyl, alkyl alkenyl, alkyl alkynyl, or alkanoyl, or taken together with the nitrogen to which it is attached, represent amidine, amide, carbamate, urea, or guanidine; and

W represents O or S.

32. The compound of claim 20, wherein Tb is represented by i and Z is absent.

33. The compound of claim 32, wherein L is absent.

34. The pharmaceutical composition of claim 20 or 21, wherein Tb is selected from xi, xii, xiv, and xv.

35. The pharmaceutical composition of claim 20 or 21, wherein Tb is selected from v, vii, and viii.

36. The pharmaceutical composition of claim 20 or 21, wherein Tb is selected from ii, iii, or iv.

37. The pharmaceutical composition of claim 20 or 21, wherein Tb is represented by x.

38. The pharmaceutical composition of claim 20 or 21, wherein Tb is represented by ix.

39. A method for the treatment or prevention of a bone disorder comprising treating a patient with a compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

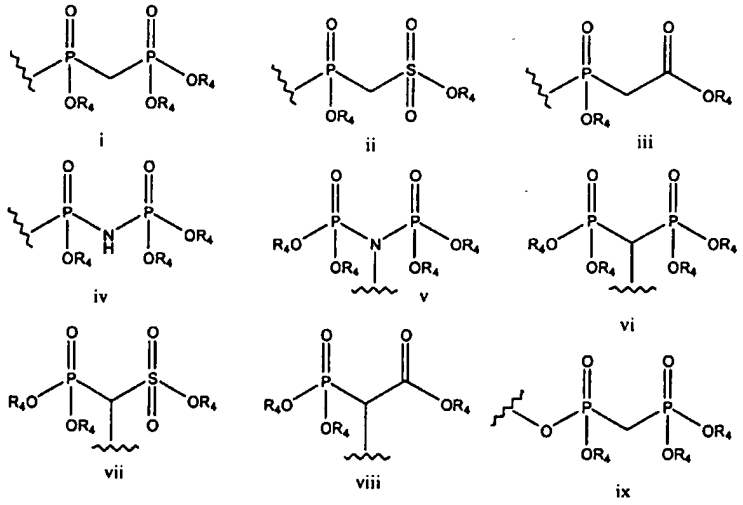
R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

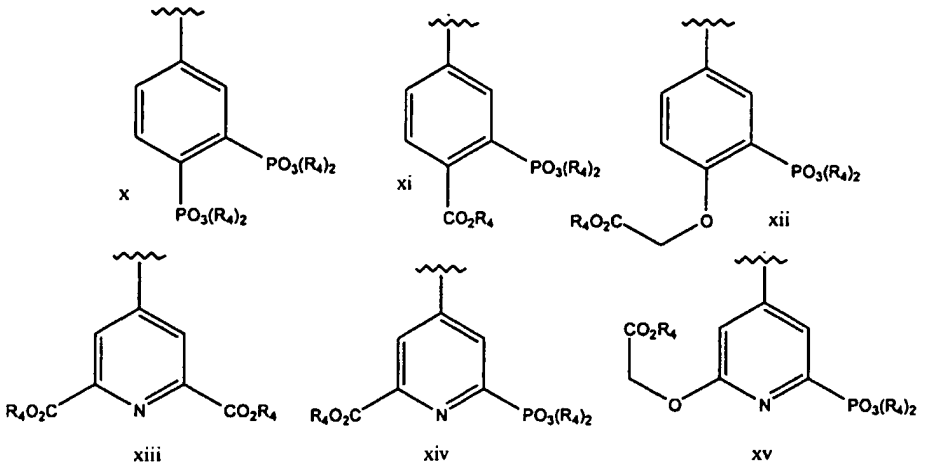
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

Tb represents a bone-targeting group selected from:





and R_4, independently for each occurrence, represents H or lower alkyl.

40. A method for the treatment or prevention of a bone disorder comprising treating a patient with a compound having the general formula **(II)**: Hc-X-K-Z-Tb, wherein

K is absent or represents $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethylene or ethyne;

p and n, independently, represent integers from 0-10.

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl.

Hc represents a heterocycle;

Tb represents a bone-targeting group selected from:

and R_4, independently for each occurrence, represents H or lower alkyl.

41. The method of claim 39 or 40, wherein the compound selectively targets osteoclasts.

42. The method of claim 39 or 40, wherein R_4 represents H for all occurrences.

43. The method of claim 39, wherein Cy represents an uncharged carbocycle or nitrogen-bearing heterocycle.

44. The method of claim 39, wherein Cy represents a phenyl, pyridyl, cyclopentyl, cyclohexyl, or a fused bicyclic ring system having between 8 and 11 atoms.

45. The method of claim 39, wherein Cy represents phenyl.

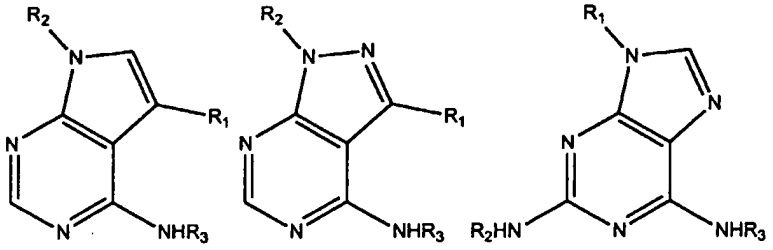
46. The method of claim 39, wherein Cy represents a bicyclic ring system, whereof L is attached to a first ring and K is attached to a second ring.

47. The method of claim 39 or 40, wherein Hc represents a bicyclic structure.

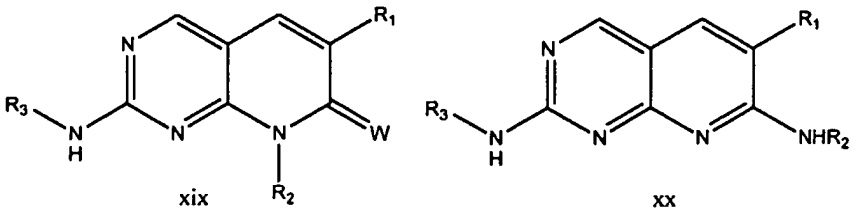
48. The method of claim 39 or 40, wherein the two rings of the bicyclic structure consist of carbon and nitrogen atoms.

49. The method of claim 39 or 40, wherein K is directly attached to a heteroatom of Hc.

50. The method of claim 39 or 40, wherein Hc is selected from:



xvi xvii xviii



xix xx

wherein one of R_1, R_2, and R_3 represents a bond to K, the others represent, independently, hydrogen, halogen, alkyl, aralkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, cycloalkyl, polycyclyl, alkyl alkenyl, alkyl alkynyl, or alkanoyl, or taken together with the nitrogen to which it is attached, represent amidine, amide, carbamate, urea, or guanidine; and

W represents O or S.

51. The method of claim 39, wherein Tb is represented by i and Z is absent.

52. The method of claim 51, wherein L is absent.

53. The method of claim 39 or 40, wherein Tb is selected from xi, xii, xiv, and xv.

54. The method of claim 39 or 40, wherein Tb is selected from v, vii, and viii.

55. The method of claim 39 or 40, wherein Tb is selected from ii, iii, or iv.

56. The method of claim 39 or 40, wherein Tb is represented by x.

57. The method of claim 39 or 40, wherein Tb is represented by ix.

58. A compound having the structure: Tb-L-V, wherein

L is absent or represents $-M_n-Y-M_p-$;

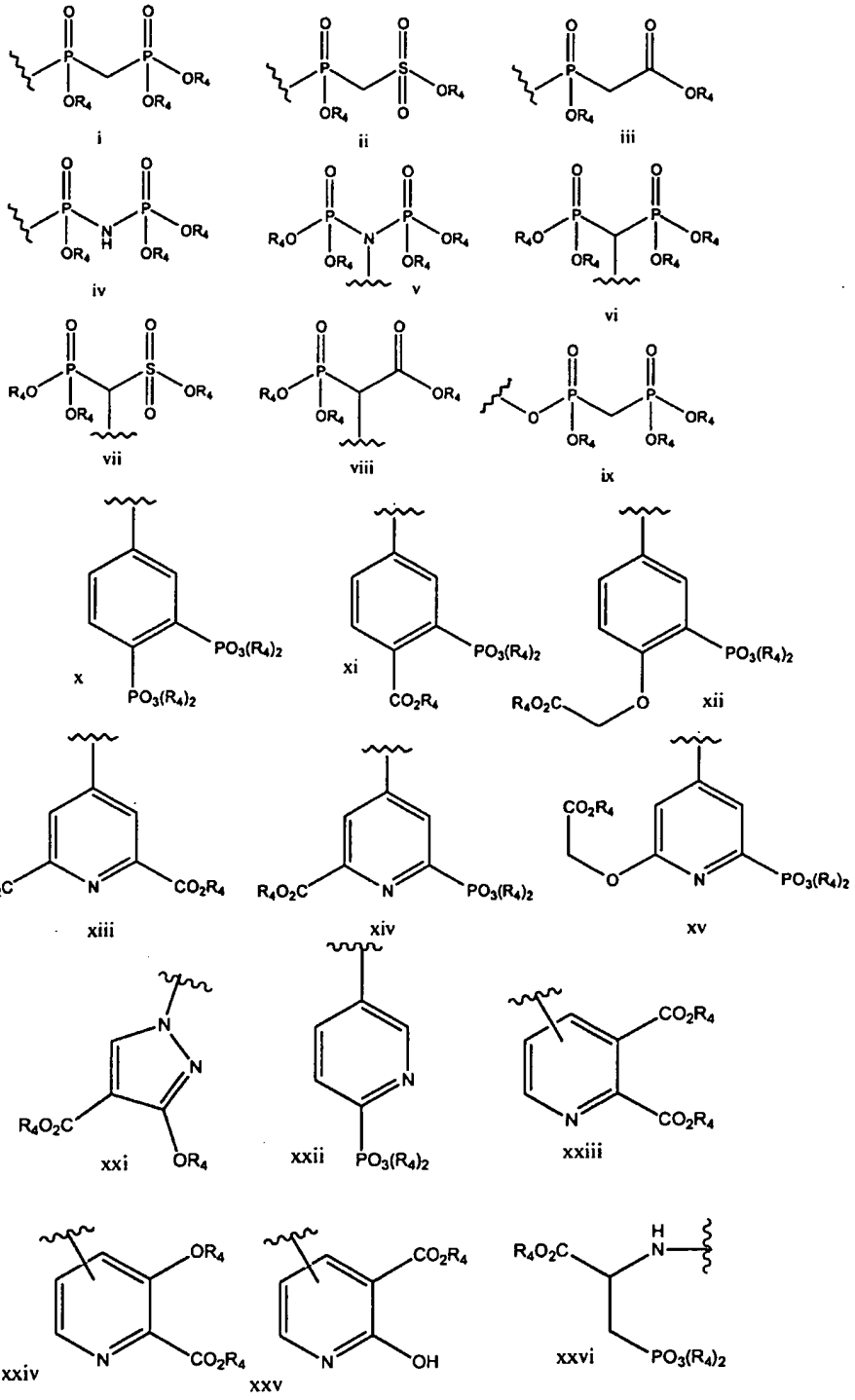
Y is absent;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

Tb represents a bone-targeting group selected from:



R_4, independently for each occurrence, represents H or lower alkyl, and

V represents OR, NR_2, or SR.

59. The compound of claim 58, wherein Tb is selected from xi, xii, xiv, and xv.

60. The compound of claim 58, wherein Tb is x.

61. The compound of claim 58, wherein Tb is xiii.

62. The compound of claim 58, wherein V represents NR_2.

63. A compound having the structure: Tb-Cy-L-V, wherein

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

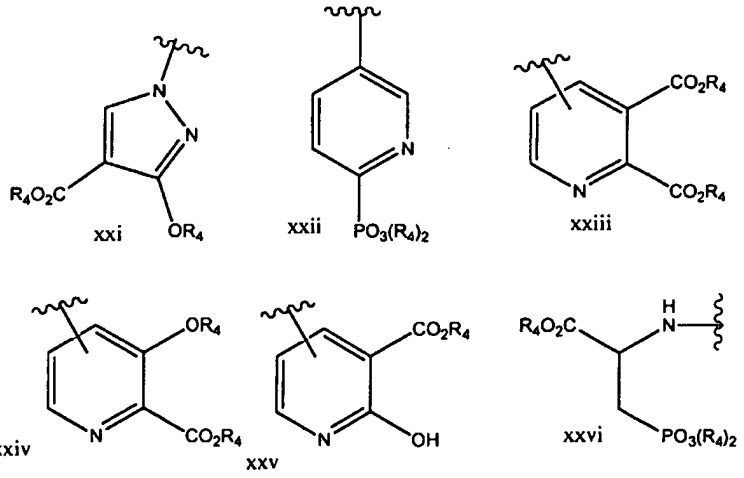
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Tb represents a bone-targeting group selected from:



R_4, independently for each occurrence, represents H or lower alkyl, and

V represents OR, NR_2, or SR.

64. The compound of claim 63, wherein Cy represents a phenyl ring.

65. The compound of claim 63, wherein V represents NR_2.

66. A compound having the structure: Tb-L-U, wherein

L is absent or represents $-M_n-Y-M_p-$;

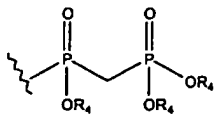
Y is absent;

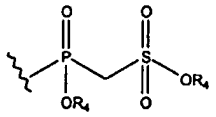
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

Tb represents a bone-targeting group selected from:


i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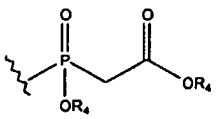
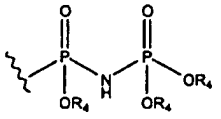

iii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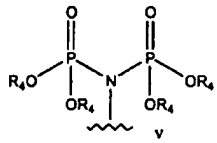
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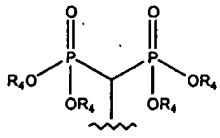
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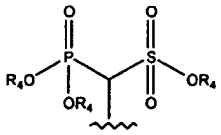
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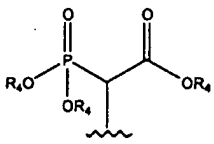
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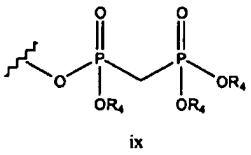
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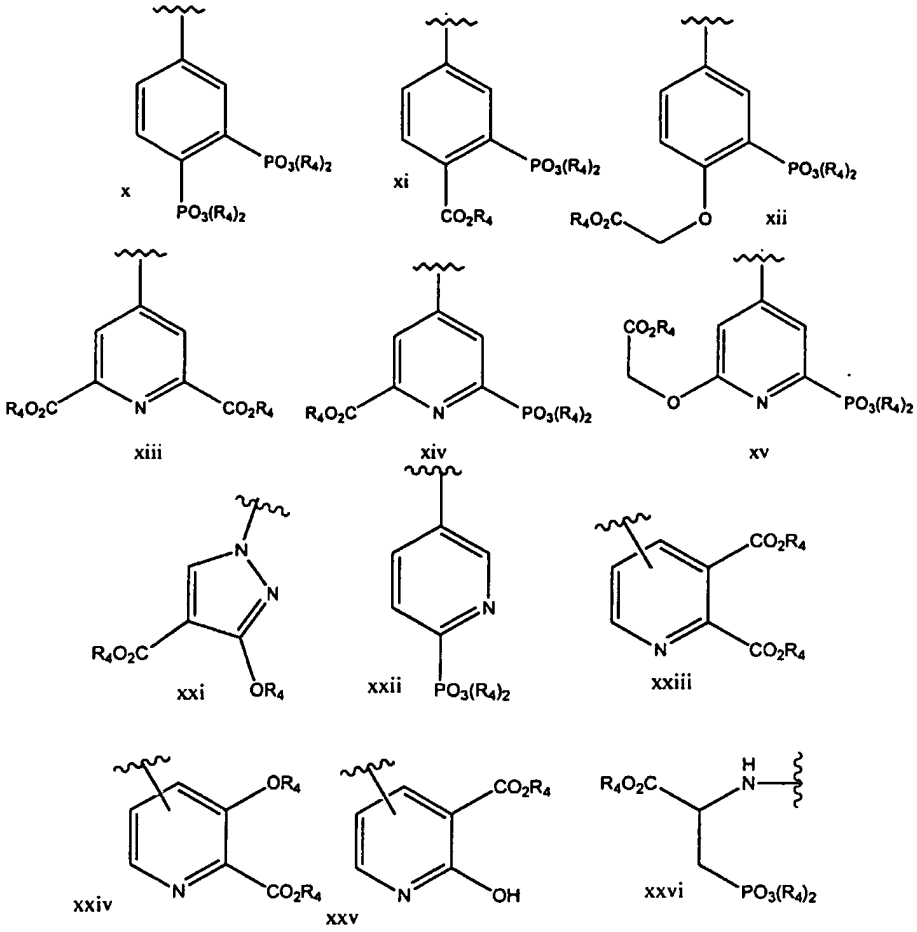


R_4, independently for each occurrence, represents H or lower alkyl, and

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group.

67. The compound of claim 66, wherein Tb is selected from xi, xii, xiv, and xv.

68. The compound of claim 66, wherein Tb is x.

69. The compound of claim 66, wherein Tb is xiii.

70. A compound having the structure: Tb-Cy-L-U, wherein

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

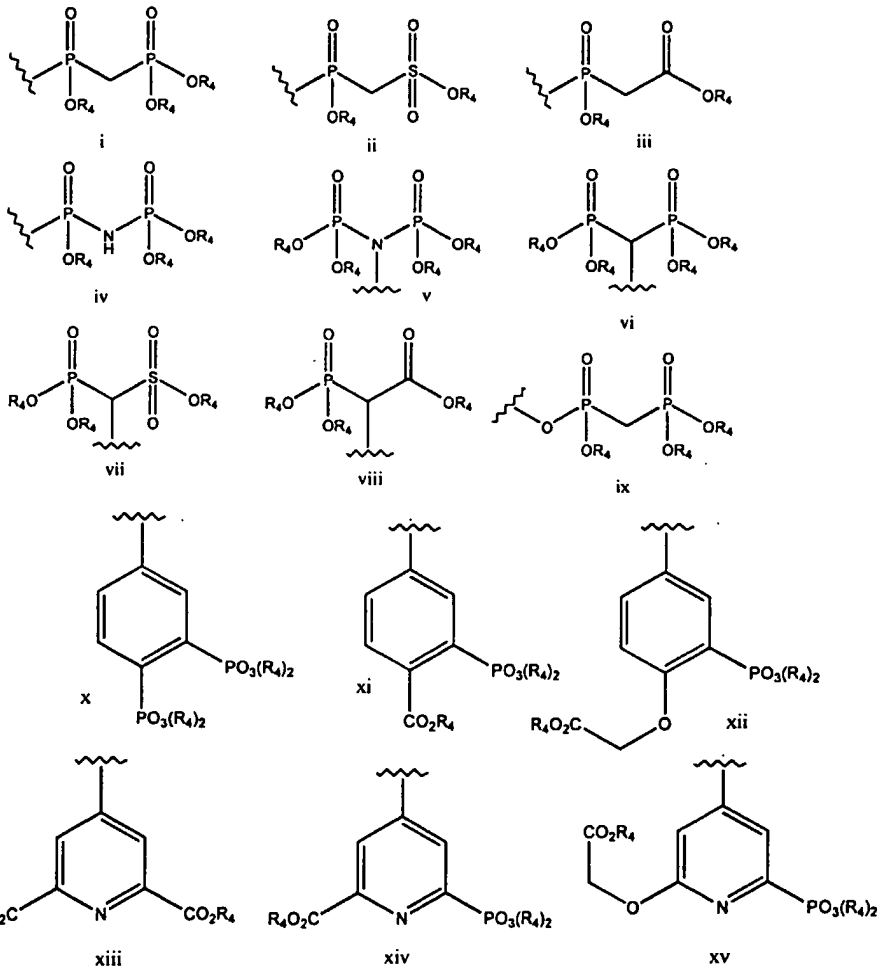
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Tb represents a bone-targeting group selected from:



R_4, independently for each occurrence, represents H or lower alkyl, and

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group.

71. A compound of claim 70, wherein Cy represents a phenyl ring.

72. A compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent -M_n-Y-M_p-;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

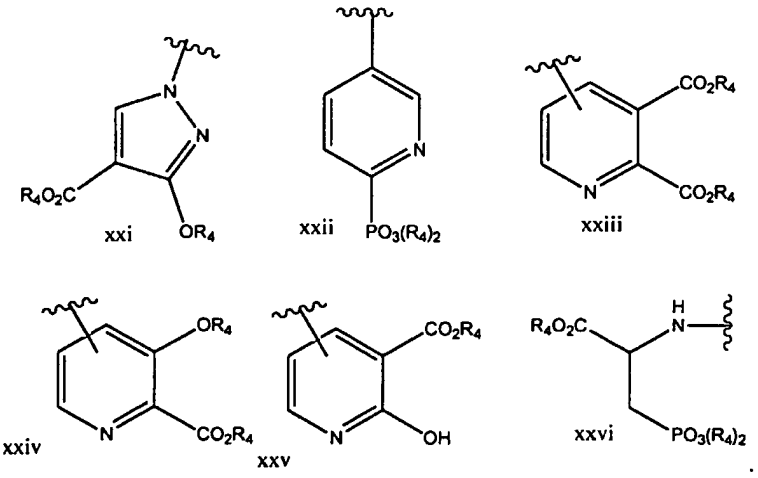
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents one of:



73. A compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent -M_n-Y-M_p-;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

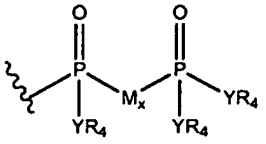
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a group selected from:



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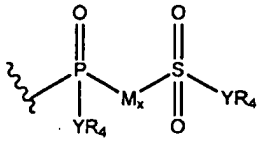

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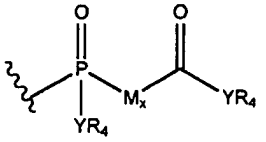

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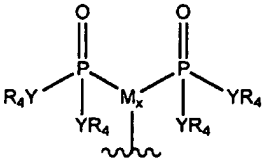

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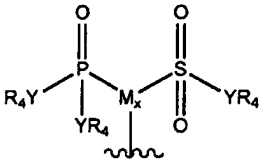

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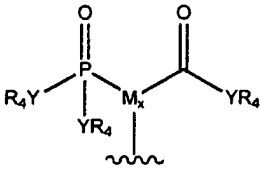

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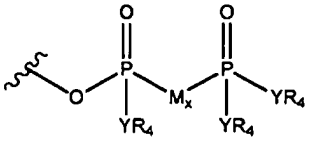
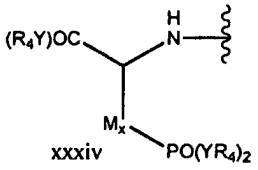


xxxiii



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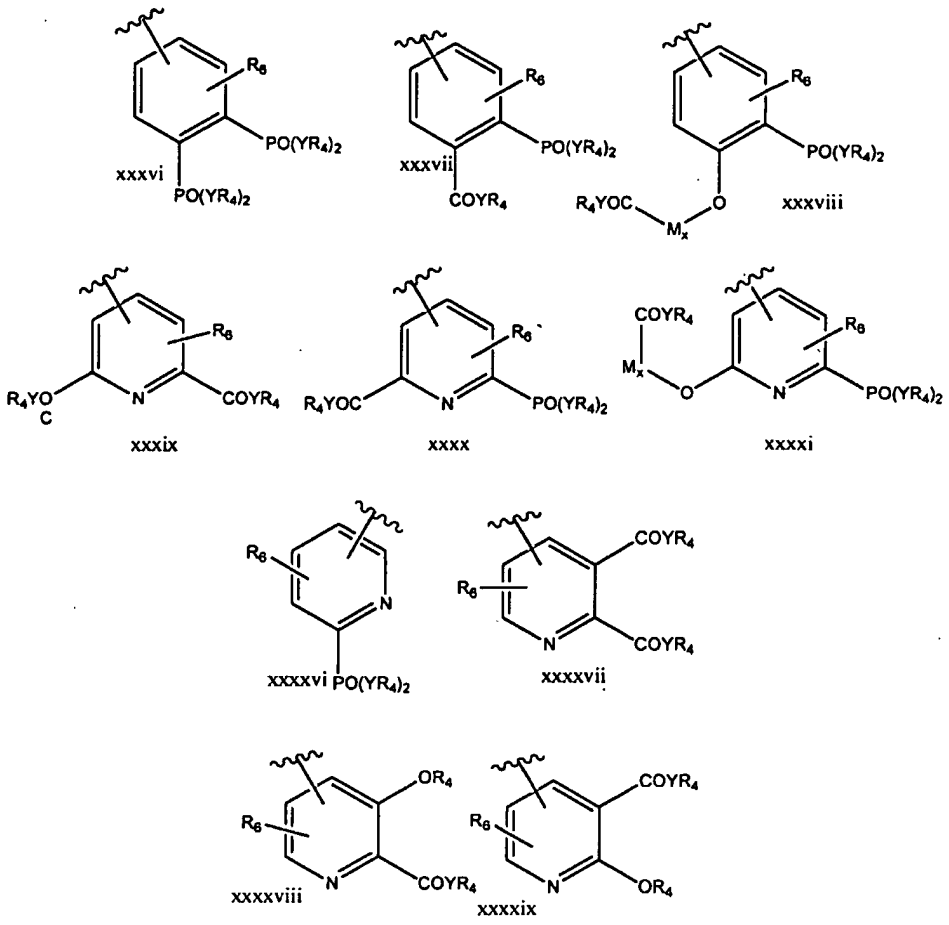


x represents 1, 2, 3, 4, 5, or 6;

each occurrence of Y is independently a covalent bond, -O-, -S-, or -N(R_J)$_2$, wherein R_J, for each occurrence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

R_6 represents from 0-3 substituents selected from halogen, lower alkyl, lower alkenyl, aryl, heteroaryl, carbonyl, thiocarbonyl, ketone, aldehyde, amino, acylamino, amido, amidino, cyano, nitro, azido, sulfonyl, sulfoxido, sulfate, sulfonate, sulfamoyl, sulfonamido, phosphoryl, phosphonate, phosphinate, -$(CH_2)_p$alkyl, -$(CH_2)_p$alkenyl, -$(CH_2)_p$alkynyl, -$(CH_2)_p$aryl, -$(CH_2)_p$aralkyl, -$(CH_2)_p$OH, -$(CH_2)_p$O-lower alkyl, -$(CH_2)_p$O-lower alkenyl, -O$(CH_2)_n$R, -$(CH_2)_p$SH, -$(CH_2)_p$S-lower alkyl, -$(CH_2)_p$S-lower alkenyl, -S$(CH_2)_n$R, -$(CH_2)_p$N(R)$_2$, -$(CH_2)_p$NR-lower alkyl, -$(CH_2)_p$NR-lower alkenyl, -NR$(CH_2)_n$R, or protected forms of the above and wherein p is 1-10; and

each occurrence of R_4 is independently hydrogen or a lower alkyl.

74. The compound of claim 73, wherein M, where it occurs in Tb, is selected from CH_2, CHJ, CHOH, and CJ_2, wherein J represents a halogen.

75. The compound of claim 73, wherein R_6 is selected from lower alkyl, hydroxyl, sulfhydryl, amino, amido, carboxyl, sulfonate, phosphonate, and salts thereof, and lower alkyl substituted with hydroxyl, sulfhydryl, amino, amido, carboxyl, sulfonate, phosphonate, and salts thereof.

76. A compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

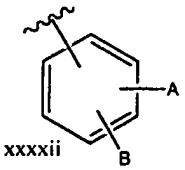
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a group having the structure:



xxxxii

A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

77. A compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

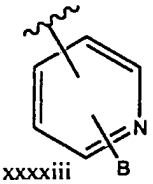
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb has the structure xxxxiii:



xxxxiii

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

78. A compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

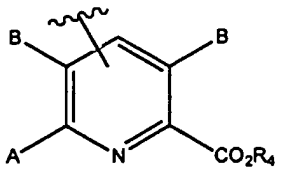
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

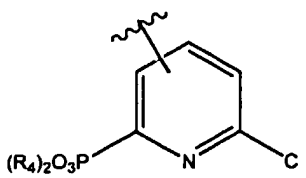
Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb has the structure xxxxiv or xxxxv:



xxxxiv



xxxxv

A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; G is absent or represents a linkage of one or two atoms;

C represents H, R_6, NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, or GSO_3R_4, such that in xxxxiv, any one occurrence of A or B is present, and the other occurrences may represent a bond to Z, H, or R_6 as desired.

79. A compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

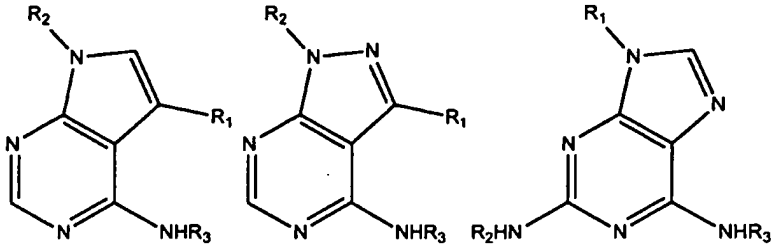
R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a heteroaryl bearing one or two B substituents, and 0-4 R_6 substituents;

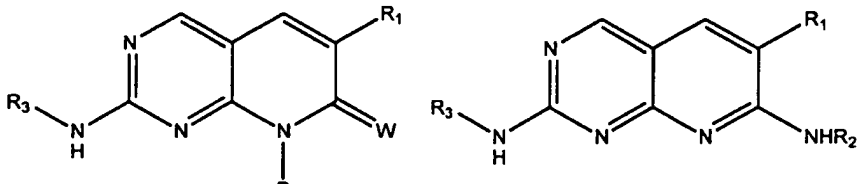
A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

80. The compound of any of claims 72-79, wherein Hc is selected from:



xvi xvii xviii



xix xx

81. The compound of any of claims 72-79, wherein, except in Tb, the compound is free of hydrolyzable linkages.

82. A compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

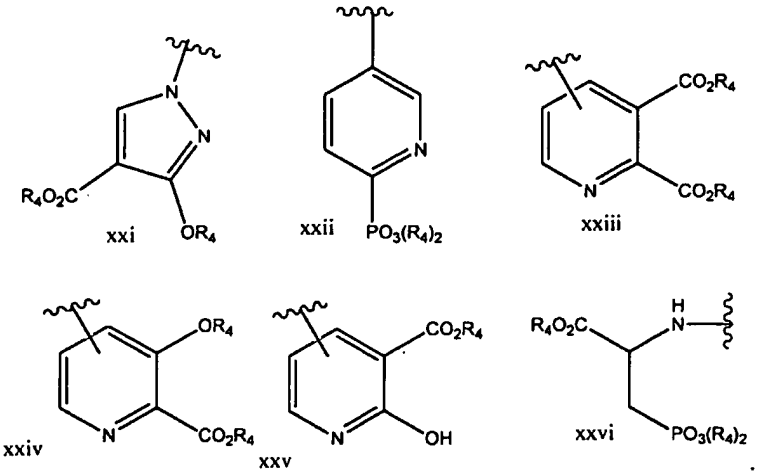
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents one of:



83. A compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

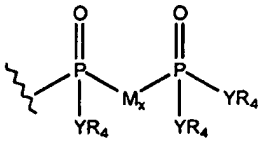
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a group selected from: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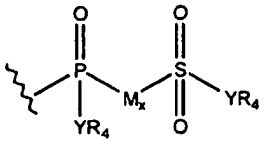
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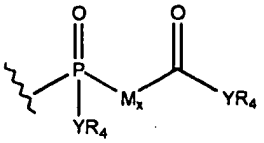
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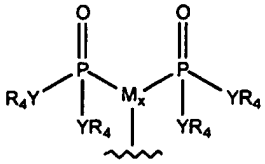
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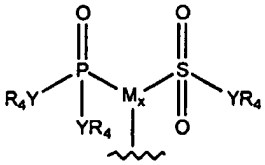
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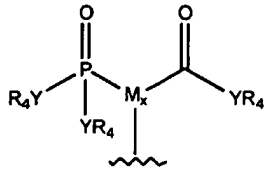
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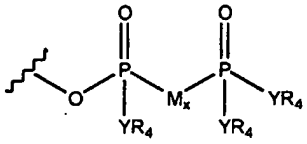
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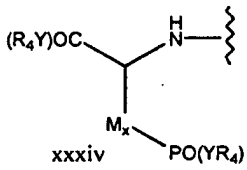
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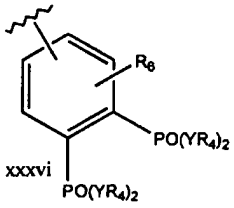
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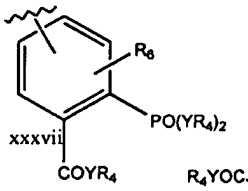
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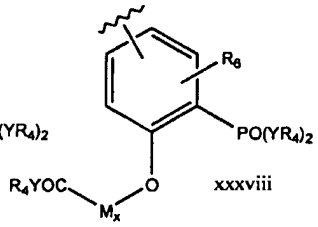
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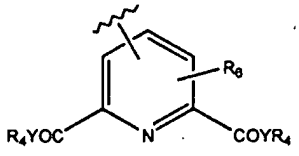
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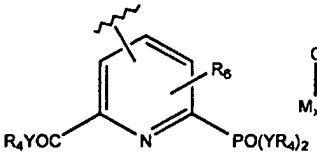
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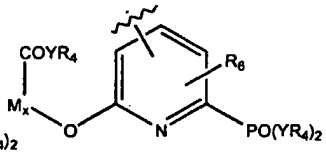
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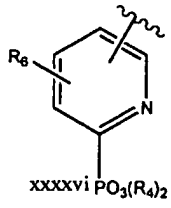
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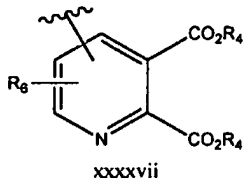
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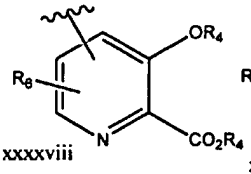
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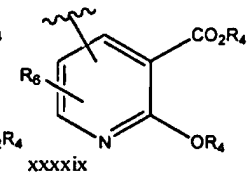

xxxxix

x represents 1 or 2, and

R_6 represents from 0-3 substituents selected from halogen, lower alkyl, lower alkenyl, aryl, heteroaryl, carbonyl, thiocarbonyl, ketone, aldehyde, amino, acylamino, amido, amidino, cyano, nitro, azido, sulfonyl, sulfoxido, sulfate, sulfonate, sulfamoyl, sulfonamido, phosphoryl, phosphonate, phosphinate, -$(CH_2)_p$alkyl, -$(CH_2)_p$alkenyl, -$(CH_2)_p$alkynyl, -$(CH_2)_p$aryl, -$(CH_2)_p$aralkyl, -$(CH_2)_p$OH, -$(CH_2)_p$O-lower alkyl, -$(CH_2)_p$O-lower alkenyl, -O$(CH_2)_n$R, -$(CH_2)_p$SH, -$(CH_2)_p$S-lower alkyl, -$(CH_2)_p$S-lower alkenyl, -S$(CH_2)_n$R, -$(CH_2)_p$N$(R)_2$, -$(CH_2)_p$NR-lower alkyl, -$(CH_2)_p$NR-lower alkenyl, -NR$(CH_2)_n$R, or protected forms of the above.

84. The compound of claim 83, wherein M, where it occurs in Tb, is selected from CH_2, CHJ, CHOH, and CJ_2, wherein J represents a halogen.

85. The compound of claim 83, wherein R_6 is selected from lower alkyl, hydroxyl, sulfhydryl, amino, amido, carboxyl, sulfonate, phosphonate, and salts thereof, and lower alkyl substituted with hydroxyl, sulfhydryl, amino, amido, carboxyl, sulfonate, phosphonate, and salts thereof.

86. A compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents -M_n-Y-M_p-;

Y is absent;

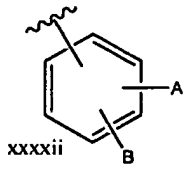
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a group having the structure:



xxxxii

A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

87. A compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

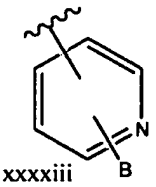
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb has the structure xxxxiii:



xxxxiii

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

88. A compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

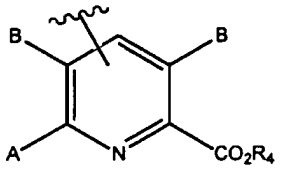
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

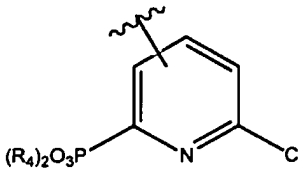
p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb has the structure xxxxiv or xxxxv:



xxxxiv



xxxxv

A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; G is absent or represents a linkage of one or two atoms;

C represents H, R_6, NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, or GSO_3R_4, such that in xxxxiv, any one occurrence of A or B is present, and the other occurrences may represent a bond to Z, H, or R_6 as desired.

89. A compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

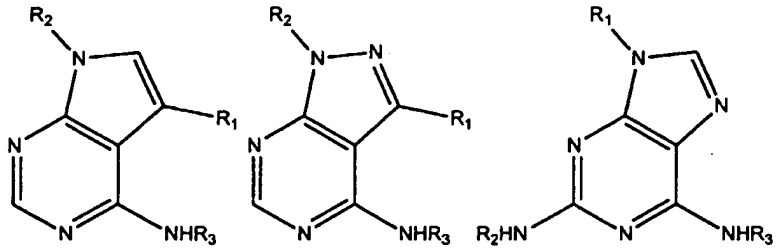
R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a heteroaryl bearing one or two B substituents, and 0-4 R_6 substituents;

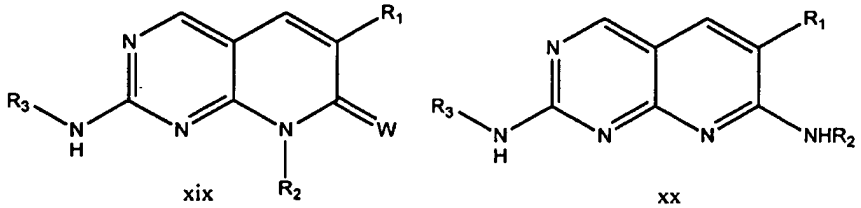
A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

90. The compound of any of claims 82-89, wherein Hc is selected from:



xvi xvii xviii



xix xx

91. The compound of any of claims 82-89, wherein L represents alkyl.

92. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

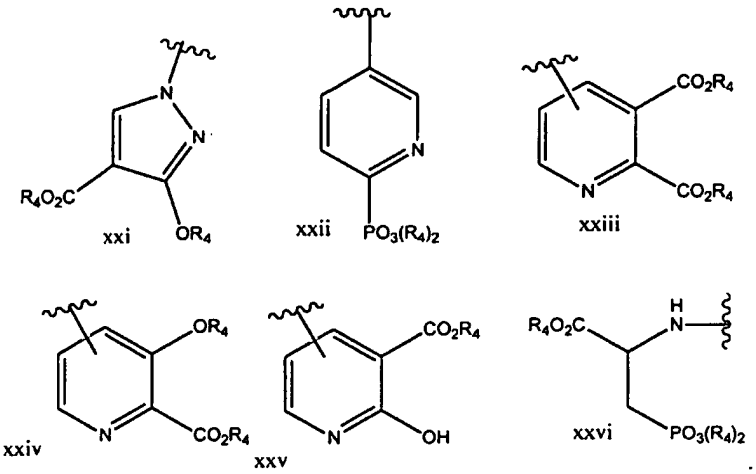
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents one of:



93. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

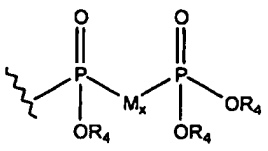
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a group selected from: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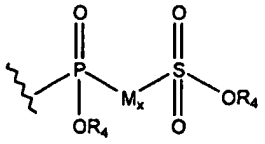
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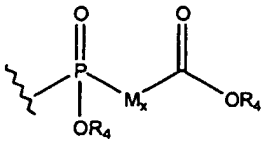
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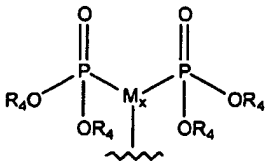
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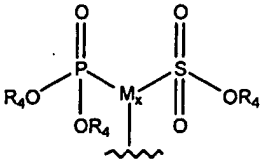
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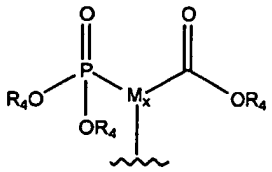
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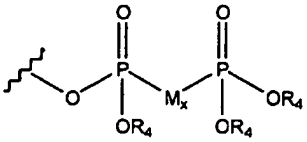
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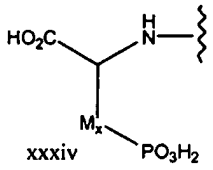
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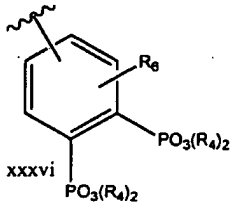
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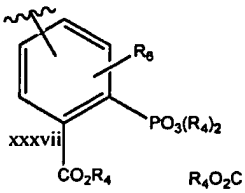
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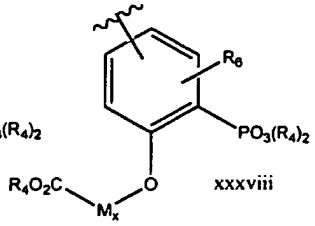
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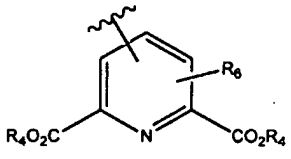
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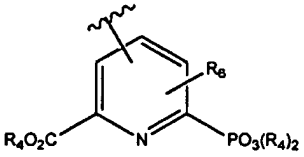
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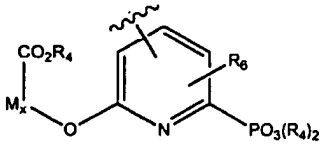
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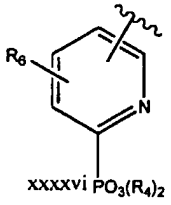
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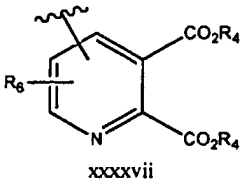
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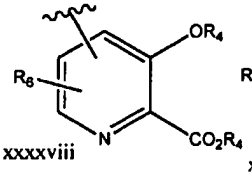
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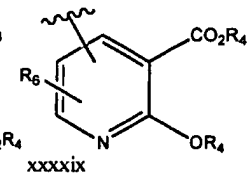

xxxxix

x represents 1 or 2, and

R_6 represents from 0-3 substituents selected from halogen, lower alkyl, lower alkenyl, aryl, heteroaryl, carbonyl, thiocarbonyl, ketone, aldehyde, amino, acylamino, amido, amidino, cyano, nitro, azido, sulfonyl, sulfoxido, sulfate, sulfonate, sulfamoyl, sulfonamido, phosphoryl, phosphonate, phosphinate, -$(CH_2)_p$alkyl, -$(CH_2)_p$alkenyl, -$(CH_2)_p$alkynyl, -$(CH_2)_p$aryl, -$(CH_2)_p$aralkyl, -$(CH_2)_p$OH, -$(CH_2)_p$O-lower alkyl, -$(CH_2)_p$O-lower alkenyl, -O$(CH_2)_n$R, -$(CH_2)_p$SH, -$(CH_2)_p$S-lower alkyl, -$(CH_2)_p$S-lower alkenyl, -S$(CH_2)_n$R, -$(CH_2)_p$N$(R)_2$, -$(CH_2)_p$NR-lower alkyl, -$(CH_2)_p$NR-lower alkenyl, -NR$(CH_2)_n$R, or protected forms of the above.

94. The compound of claim 92, wherein M, where it occurs in Tb, is selected from CH_2, CHJ, CHOH, and CJ_2, wherein J represents a halogen.

95. The compound of claim 92, wherein R_6 is selected from lower alkyl, hydroxyl, sulfhydryl, amino, amido, carboxyl, sulfonate, phosphonate, and salts thereof, and lower alkyl substituted with hydroxyl, sulfhydryl, amino, amido, carboxyl, sulfonate, phosphonate, and salts thereof.

96. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent -M_n-Y-M_p-;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

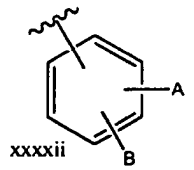
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a group having the structure:



xxxxii

A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

97. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent $-M_n-Y-M_p-$;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

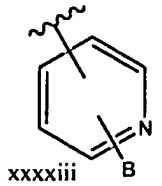
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb has the structure xxxxiii:



xxxxiii

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

98. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent -M_n-Y-M_p-;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

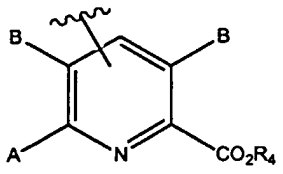
p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

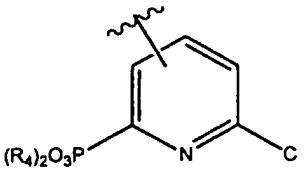
Hc represents a heterocycle;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb has the structure xxxxiv or xxxxv:



xxxxiv



xxxxv

A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; G is absent or represents a linkage of one or two atoms;

C represents H, R_6, NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, or GSO_3R_4, such that in xxxxiv, any one occurrence of A or B is present, and the other occurrences may represent a bond to Z, H, or R_6 as desired.

99. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the general formula **(I)**: Hc-X-K-Cy-L-Z-Tb, or **(II)**: Hc-X-K-Z-Tb, wherein

L and K, independently, are absent or represent -M_n-Y-M_p-;

X, Y, and Z, independently, are absent or represent NR, O, or S;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene or ethyne;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

Cy represents a substituted or unsubstituted aryl, heterocyclyl, heteroaryl, or cycloalkyl;

Hc represents a heterocycle;

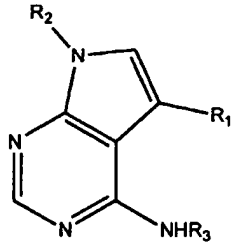
R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a heteroaryl bearing one or two B substituents, and 0-4 R_6 substituents;

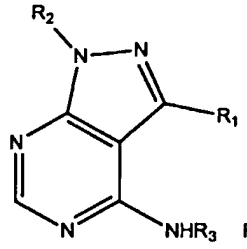
A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

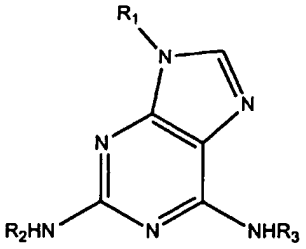
100. The method of any of claims 92-99, wherein Hc is selected from:



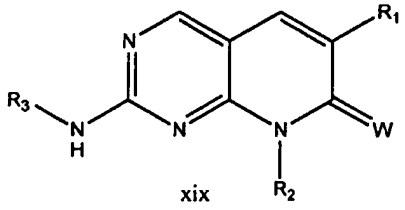
xvi



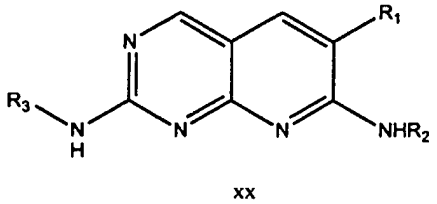
xvii



xviii



xix



xx

101. The method of any of claims 92-99, wherein, except in Tb, the compound is free of hydrolyzable linkages.

102. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

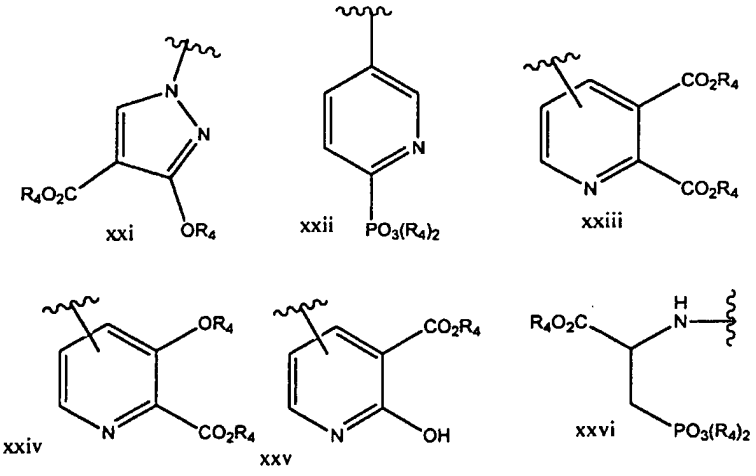
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents one of:



103. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

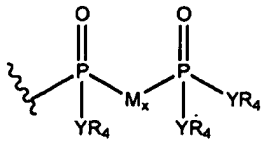
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a group selected from:



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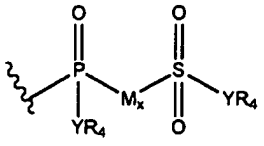

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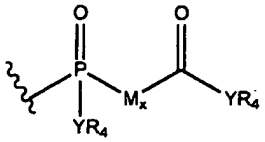

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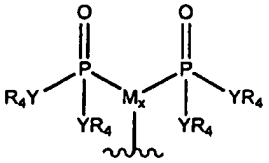

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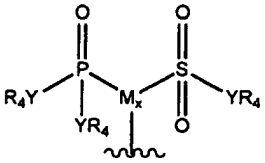

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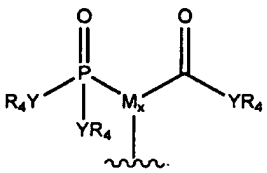
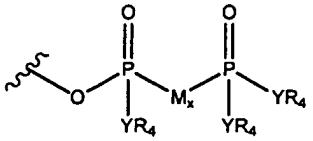
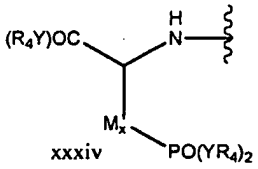


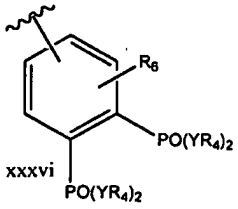
xxxii



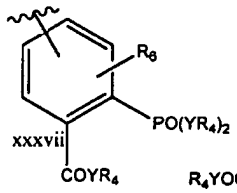
xxxiii



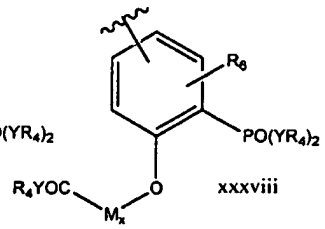
xxxiv



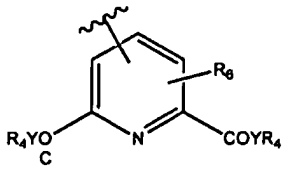
xxxvi



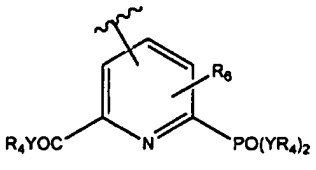
xxxvii



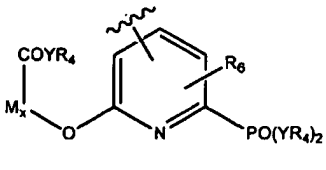
xxxviii



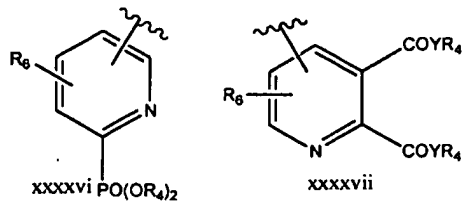
xxxix



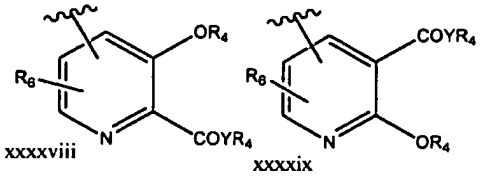
xxxx



xxxxi



xxxxvi xxxxvii



xxxxviii xxxxix

x represents 1, 2, 3, 4, 5, or 6;

each occurrence of Y is independently a covalent bond, -O-, -S-, or -$N(R_J)_2$, wherein R_J, for each occurrence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

R_6 represents from 0-3 substituents selected from halogen, lower alkyl, lower alkenyl, aryl, heteroaryl, carbonyl, thiocarbonyl, ketone, aldehyde, amino, acylamino, amido, amidino, cyano, nitro, azido, sulfonyl, sulfoxido, sulfate, sulfonate, sulfamoyl, sulfonamido, phosphoryl, phosphonate, phosphinate, -$(CH_2)_p$alkyl, -$(CH_2)_p$alkenyl, -$(CH_2)_p$alkynyl, -$(CH_2)_p$aryl, -$(CH_2)_p$aralkyl, -$(CH_2)_p$OH, -$(CH_2)_p$O-lower alkyl, -$(CH_2)_p$O-lower alkenyl, -$O(CH_2)_nR$, -$(CH_2)_p$SH, -$(CH_2)_p$S-lower alkyl, -$(CH_2)_p$S-lower alkenyl, -$S(CH_2)_nR$, -$(CH_2)_pN(R)_2$, -$(CH_2)_p$NR-lower alkyl, -$(CH_2)_p$NR-lower alkenyl, -$NR(CH_2)_nR$, or protected forms of the above; and

each occurrence of R_4 is independently hydrogen or a lower alkyl.

104. The method of claim 103, wherein M, where it occurs in Tb, is selected from CH_2, CHJ, CHOH, and CJ_2, wherein J represents a halogen.

105. The method of claim 103, wherein R_6 is selected from lower alkyl, hydroxyl, sulfhydryl, amino, amido, carboxyl, sulfonate, phosphonate, and salts thereof, and lower alkyl substituted with hydroxyl, sulfhydryl, amino, amido, carboxyl, sulfonate, phosphonate, and salts thereof.

106. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

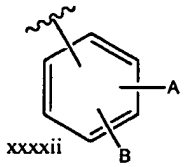
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a group having the structure:



xxxxii

A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

107. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

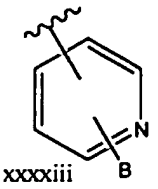
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb has the structure xxxxiii:



xxxxiii

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

108. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

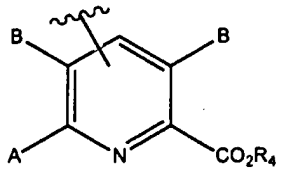
M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

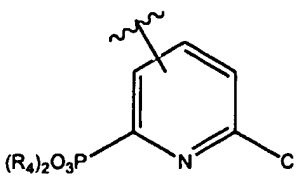
p and n, independently, represent integers from 0-10;

R_4, independently for each occurrence, represents H or lower alkyl; and

Tb has the structure xxxxiv or xxxxv:



xxxxiv



xxxxv

A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; G is absent or represents a linkage of one or two atoms;

C represents H, R_6, NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, or GSO_3R_4, such that in xxxxiv, any one occurrence of A or B is present, and the other occurrences may represent a bond to Z, H, or R_6 as desired.

109. A method for treating or preventing a bone disorder comprising a pharmaceutically acceptable excipient and a compound having the formula: V-L-Cy-Tb, V-L-Tb, U-L-Cy-Tb, or U-L-Tb, wherein

U represents a sulfonate ester, halogen, formyl, or a suitable leaving group;

V represents OR, NR_2, or SR;

L is absent or represents $-M_n-Y-M_p-$;

Y is absent;

M represents, independently for each occurrence, a substituted or unsubstituted methylene group, or two M taken together represent substituted or unsubstituted ethene;

R represents, independently for each occurrence, H or substituted or unsubstituted aryl, heterocyclyl, heteroaryl, aralkyl, alkenyl, or alkyl;

p and n, independently, represent integers from 0-10;

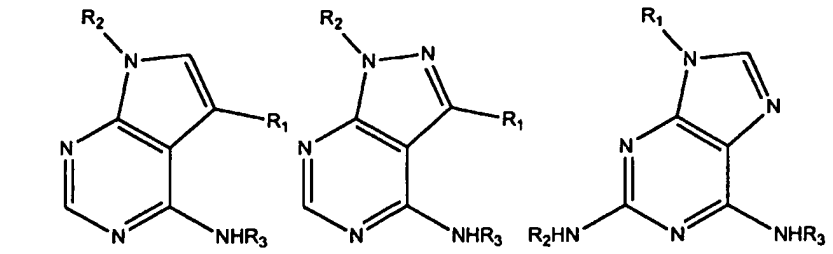
R_4, independently for each occurrence, represents H or lower alkyl; and

Tb represents a heteroaryl bearing one or two B substituents, and 0-4 R_6 substituents;

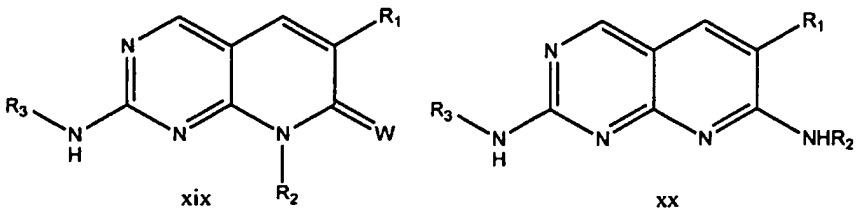
A represents a group selected from $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4;

B represents a group selected from NH_2, OH, $GPO_3(R_4)_2$, GCO_2R_4, and GSO_3R_4; and G is absent or represents a linkage of one or two atoms.

110. The method of any of claims 102-109, wherein Hc is selected from:



xvi xvii xviii



xix xx

111. The method of any of claims 102-109, wherein L represents alkyl.

INTERNATIONAL SEARCH REPORT

Inten al Application No
PCT/US 00/34487

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/6512

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 170 228 A (BOEHRINGER MANNHEIM GMBH) 5 February 1986 (1986-02-05) page 14, compound 10 from the top page 1, line 1 -page 6, line 20	2,4,11, 21,23, 30,73, 74,93
X	example 1 ---	73,74
X	WO 94 09017 A (UPJOHN CO ;DUNN COLIN JOHN (US); CHIN JIA EN (US); NUGENT RICHARD) 28 April 1994 (1994-04-28) page 7 f) page 1, line 1 - line 14; claim 18E; example 25	2,4,21, 93
X	claims 1-12; examples 1-16 --- -/--	73,74

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2001	18.04.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Richter, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 186 405 A (PROCTER & GAMBLE) 2 July 1986 (1986-07-02) examples page 1, line 1 -page 9, line 4; claims 1-33	2,4,21, 23,73, 74,93
X	EP 0 084 822 A (SCHERING AG) 3 August 1983 (1983-08-03) claims 3-16	73,74
X	EP 0 304 962 A (PROCTER & GAMBLE) 1 March 1989 (1989-03-01) page 1, line 5 -page 5, line 10; claims 2,3	2,4,9, 10,21, 23,28, 29,73,93
X	EP 0 085 321 A (SCHERING AG) 10 August 1983 (1983-08-10) page 1 -page 2; example 14	2,21,73, 93
X	US 5 866 556 A (HEIKKILAE-HOIKKA MARJAANA ET AL) 2 February 1999 (1999-02-02) the whole document	2,3,21, 22,73,93

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 00/34487

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 93 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1, 5-8,13-20,24-27,32-72,74,76-92,94-111
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 5-8,13-20,24-27,32-72,74,76-92,94-111

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

Present independent claims 1,2,20,21,39,58,63,66,70,72,73,76-79,82,83,86-89,92,93,98,98,99,102,103,106,108,109 relate to an extremely large number of possible compounds and methods. In fact, the claims contain so many options, variables, and possible permutations
that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise).

Amongst others these claims relate to compounds, products and methods defined (inter alia)

by reference to the following parameter:
"wherein Hc-X-K is free of hydrolyzable linkages".
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the definition in the description, page 6, lines 5-9.

A definition of Tb is missing in claim 40. Hence, no search was possible for this claim and dependent claims 41,42,47-50.

For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to claims 2-4,9-12,21-23,28-31,73,74,93 in which the compound has the formula (II) and Tb has the meaning vi or xxx.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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